

# Hemodynamics during rest and behavioral stress in normotensive men at high risk for hypertension

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## Abstract

Persons at risk for hypertension may show elevated blood pressure (BP) at rest and during mental stress; however, the hemodynamics underlying the BP of those persons at high risk are not well characterized. We chose 21 high risk and 21 low risk men using their parental hypertension history and resting systolic blood pressures on two screenings. Then, on a day of extended rest versus a day with prolonged mental arithmetic and reaction time tasks, we examined whether high risk BP elevations reflected greater vascular resistance or cardiac output. High risk men had raised systolic/diastolic pressures ( $F_s = 74/15$ ,  $p_s < .0001/.0001$ ) and higher vascular resistance ( $F = 6.6$ ,  $p < .02$ ) with minimal differences in heart rate and cardiac output. This finding implicates vascular resistance as the altered element in BP control in these high risk men tested in a familiar environment with minimal task-related threat.

**Descriptors:** Hypertension, Blood pressure, Cardiac output, Vascular resistance, Impedance cardiography, Mental stress

The present report examines the hemodynamic basis of blood pressure (BP) elevations in men at high risk for hypertension (HiRsk). Essential hypertension is a significant cause of organ damage, contributing to cardiovascular disease morbidity and mortality, and BP responses to behavioral stress may contribute to disease progression (Everson, Kaplan, Goldberg, & Salonen, 1996; Lovallo & Wilson, 1992a, 1992b). As an aid to depicting the development of hypertension, an accurate description of cardiac output and vascular resistance in HiRsk persons is critical to evaluating competing models of hypertension and the potential for behavioral factors to contribute to the development of the disease.

In previous work, 220 young men visited the laboratory for screening, and we selected HiRsk individuals with both a positive parental history (PH+) and resting systolic BP  $\geq 125$  mmHg. The HiRsk had elevated resting heart rates (HRs) and diastolic BPs, and they had greater HR and BP increases to mental arithmetic stress than did low risk men (LoRsk) (al'Absi, Everson, & Lovallo, 1995; Everson, Lovallo, Sausen, & Wilson, 1992). We do not know if the HiRsk BP elevations in that sample were due to altered cardiac output, vascular resistance, or both. In a later study, HiRsk men had higher systemic vascular resistance during rest and mental stress (Marrero, Pincomb, al'Absi, & Lovallo, 1997). However,

the sample was relatively small, and parental history was not always verified by physician report.

There are two primary models of hypertension development (Lovallo & Wilson, 1992a, 1992b). The hyperkinetic circulatory model postulates an inappropriately elevated cardiac output with normal vascular resistance (Julius, Esler, & Randall, 1975). The presumed excess cardiac output is said to cause stress on resistance vessels, thus causing thickened walls and narrowed internal diameters and leading to permanently elevated vascular resistance (Folkow, 1982). Thus, altered blood vessel architecture is secondary to persistently elevated cardiac output.

The second model focuses on the action of intrinsic growth factors that would directly cause thickening of blood vessels and the left ventricle at all stages of the disease (Folkow, 1990; Lee, Bohm, Paul, & Ganten, 1993; Lovallo & Wilson, 1992a, 1992b), even in the presence of normal hemodynamic stimuli (Anversa, Capasso, Olivetti, & Sonnenblick, 1992; Bergbrant, Hansson, & Jern, 1993; Korner, Angus, Bobik, & Jennings, 1991). These morphologic changes appear to precede significant BP elevations (Devereux, de Simone, Koren, Roman, & Laragh, 1991; Frohlich et al., 1992) and lead to elevated vascular resistance.

Both models recognize an increased central nervous system activation and sympathetic outflow in the prehypertensive state. The heightened central nervous system reactivity of HiRsk persons complicates the measurement of hemodynamic differences between HiRsk and LoRsk persons. Previous hemodynamic studies have used invasive methods to measure cardiac output and have tested volunteers in a novel setting, leading us to speculate that participants were tested in an anxious state. Increased anxiety can cause

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fight-flight reactions characterized by increased cardiac output and low vascular resistance (Lovallo et al., 1985), the hemodynamic pattern seen in previous tests of high risk persons. This pattern may not represent the usual state of their cardiovascular systems.

The present study sought to minimize anxiety and threat during nonstress portions of testing to dissociate the reactivity tendencies of HiRsk men from their underlying hemodynamic pattern. The stress day was compared with a rest day on which participants were monitored while relaxed and awake without behavioral demands. Based on previous findings, we expected vascular resistance to be elevated in the HiRsk group with no difference in cardiac output.

## Method

### Participants

Participants were 42 healthy male, Caucasian volunteers (21 HiRsk, 21 LoRsk), aged 21–35 years. Volunteers were considered HiRsk if they had  $125 \text{ mmHg} \leq \text{systolic BP} < 140 \text{ mmHg}$  and one or two parents with essential hypertension, as confirmed by physician report, thereby matching the risk profile of a larger group of volunteers in our previous studies (al'Absi et al., 1995; Everson et al., 1992). LoRsk participants had average resting systolic BP  $< 125 \text{ mmHg}$  and no parental hypertension, again confirmed by physician report.

All participants met the following screening criteria: average BP  $< 140/90 \text{ mmHg}$ , body weight  $\pm 20\%$  of ideal by Metropolitan Life Insurance Company norms, self-reported good health, no current prescription medications, no prior treatment for hypertension, alcohol consumption  $< 15$  drinks/week, smoking  $\leq 10$  cigarettes/day, and coffee or equivalent caffeine use of  $< 5$  cups/day. The final sample included two HiRsk smokers (1–4 cigarettes/month and 1 cigarette/day). Volunteers signed an informed consent form approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and the Veterans Affairs Medical Center and were paid for their participation. Participant characteristics are shown in Table 1.

**Table 1.** Participant Demographic Characteristics

	LoRsk	HiRsk	<i>t</i>
Anthropometric characteristics			
Age (years)	24.6 (0.8)	25.5 (0.9)	<1
Weight (kg)	77 (4.7)	87 (4.8)	1.52
Height (cm)	172 (2.7)	176 (2.8)	<1
BMI ( $\text{g}/\text{cm}^2$ )	2.6 (0.21)	2.9 (0.21)	<1
Body fat (%)	18 (0.9)	17.2 (0.8)	<1
First screening session			
SBP (mmHg)	116 (2.1)	134 (2.1)	6.32***
DBP (mmHg)	65 (1.8)	74 (1.9)	3.55**
HR (bpm)	66 (2.6)	67 (2.7)	<1
Second screening session			
SBP (mmHg)	112 (2.0)	127 (2.0)	5.23***
DBP (mmHg)	63 (1.9)	70 (1.9)	2.39*
HR (bpm)	67 (2.3)	66 (2.3)	<1

Note: BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; entries show mean ( $\pm \text{SEM}$ );  $n = 21$  in each group.

\* $p < .025$ . \*\* $p < .001$ . \*\*\* $p < .0001$ .

### Procedure

The 2 screening days were always held before the 2 test days. Before each session, participants abstained from alcohol for 24 hr and from caffeine for 12 hr. Test sessions were held in the morning.

During screenings, the participant relaxed for 5 min while seated, followed by three simulated casual BPs taken over 5 min, followed by a 15-min series of 7–8 BPs taken at 2-min intervals, as previously described (Everson et al., 1992). The average systolic BP over the 15 min was used to determine risk group classification.

On study days, participants were instrumented for recording of cardiovascular function, had an intravenous catheter inserted, and signed the consent form. Following 30 min of adaptation time and placebo administration, the present protocol included rest (60 min), tasks or continued rest (60 min), and continued rest or recovery (60 min) for 180 min of observation. A 5-min rest room break occurred at 60 min into the protocol.

### Tasks

The task period consisted of alternating 15-min periods of mental arithmetic and reaction time. Task orders and task and rest days were counterbalanced across participants within groups.

Reaction time consisted of rapidly depressing a response key to an unsignaled visual cue (the word *go*) presented 60 times in 15 min by video monitor. To maximize alertness, the cues were presented at unpredictable intervals ranging from 4 to 30 s ( $M = 15$  s). Participants were challenged with a reward incentive of \$0.25 for each response of  $< 270$  ms. The number of bonuses earned was continuously displayed on the monitor.

Each participant was also administered a moderately difficult continuous mental arithmetic task in three 5-min blocks in alternate 15-min periods. Given a three-digit number, the participant added the digits and then added the resultant sum to the original number. This calculation was then performed on the new sum, and so forth. Each answer was spoken via intercom to the experimenter, who informed the participant when an incorrect response was given.

### Apparatus and Dependent Variables

All BPs and HRs were measured by a Dinamap oscillometric monitor (Critikon, Tampa, FL) with the cuff placed on the left arm.

Stroke volume was measured using an impedance cardiograph system (Minnesota Impedance Cardiograph Model 904B, Minneapolis, MN) coupled to an analog-to-digital converter and microcomputer to provide ensemble-averaged waveforms of the primary impedance signal ( $\Delta Z$ ) and its first derivative ( $dZ/dt$ ). The averaged  $dZ/dt$  and the electrocardiogram were used to calculate stroke volume using the equation of Kubicek et al. (1974). Band electrode placement followed standard guidelines (Sherwood et al., 1990). Distances between the recording electrodes were held constant for each participant across study days.

Dependent variables included systolic BP, diastolic BP, mean arterial pressure (MAP), HR obtained from the Dinamap monitor, and stroke volume (SV) from impedance data. Cardiac output (CO) and systemic vascular resistance (SVR) were derived as follows:  $\text{CO}(\text{L}/\text{min}) = \text{SV} \cdot \text{HR}$ , and  $\text{SVR}(\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}) = \text{MAP}/\text{CO} \cdot 80$ .

Stroke volumes by impedance cardiography have been validated for this laboratory against nuclear ventriculography (Wilson, Sung, Pincomb, & Lovallo, 1989). The ensemble-averaged stroke volume has been validated against hand-scored beat-to-beat records (Everson, Lovallo, Pincomb, Kizakevich, & Wilson, 1991). In addition, computer-averaged cardiac output measurements by impedance cardiography have been validated against simultaneous

thermodilution measurements (Pickett & Buell, 1992). Impedance cardiography has been shown to be valid for between-group comparisons of absolute cardiac output (Mehlsen et al., 1991) and has been used by others to compare hemodynamic profiles of groups at different levels of risk for hypertension (Sherwood, Hinderliter, & Light, 1995). Day-to-day reliabilities of stroke volume measurements were checked at rest using a 2 Groups  $\times$  4 Days analysis of variance (ANOVA). None of the terms (groups, days, or Groups  $\times$  Days) were significant,  $F_s < 1$ . At baseline, Pearson  $r_s = .87$  on rest days and  $.83$  on task days, indicating stable measurements within participants across days.

Blood was collected by syringe every 15 min for measurement of caffeine, adrenocorticotropin, and cortisol. No group differences were found, and the effects of caffeine on these variables have been reported elsewhere (Lovallo et al., 1996).

Participants rated their moods using 12 10-point visual analog scales (boredom, concentration, control, distress, effort, interest, impatience, irritability, pleasantness, stimulation, tiredness, and tension) adapted from Forsman (see Lundberg & Frankenhaeuser, 1980). Distress and activation subscales were computed based on previous factor analyses. Distress was the average of reports of impatience, irritability, distress, pleasantness, and control, with the last two reversely scored. Activation was calculated as the average of reported effort, tension, concentration, interest, and stimulation.

#### Data Reduction and Analysis

Variables derived from the Dinamap monitor were sampled every 2 min. Impedance-derived measurements were obtained over two 1-min intervals every 5 min. Data were then averaged to represent the 15-min periods during rest and tasks. Preliminary analyses comparing responses with the mental arithmetic versus the reaction time task indicated that mental arithmetic led to greater BP rises and increases in CO. However, the groups did not differ in response to either task, and there were no differences between groups over repetitions of the tasks. For clarity of presentation, the alternating 15-min periods of the two tasks were averaged into two 30-min task periods and compared with corresponding periods of the rest day.

Mood ratings were taken at the end of adaptation, following the postplacebo rest, after the tasks, and at the end of recovery.

In the primary caffeine study design, participants were screened twice and then tested on 2 days of placebo and 2 days of caffeine administration, in counterbalanced order. Therefore, including the screenings, half of the data are from Days 3 and 4 and half from Days 5 and 6 in the laboratory. The original sample included 48 participants (24 HiRsk and 24 LoRsk). Impedance data for six participants (3 HiRsk and 3 LoRsk) were unusable, and these data were dropped from all subsequent analyses, leaving a final sample of 21 HiRsk and 21 LoRsk participants.

Group demographic characteristics were compared using Student's  $t$  test. BPs and HRs were compared between groups over the two screening sessions in a set of 2 Groups  $\times$  2 Days ANOVAs. In the main study, cardiovascular activity was tested using 2 Risk Groups (low, high)  $\times$  2 Days (rest, tasks)  $\times$  4 Periods (baseline, Period 1, Period 2, recovery) repeated measures MANOVAs. Mood reports were compared using 2 Risk Groups (low, high)  $\times$  2 Days (rest, tasks)  $\times$  4 Periods (baseline, pretask, posttask, recovery) repeated measures multivariate MANOVAs. Tests of the periods factor were based on Wilks's lambda.

In accord with the primary questions, simple effects and simple interaction effects tests were conducted within the larger primary ANOVAs. Because our main focus was to contrast risk groups over

time at rest and during tasks, we conducted analyses of the simple Groups  $\times$  Periods (baseline, Period 1, Period 2, recovery) interactions separately on the rest day and on the task day (Winer, 1972). This method resulted in heterogeneous sources of variation entering into the error term, and degrees of freedom were calculated using Satterthwaite's approximation as outlined by Winer (1972, pp. 380–384). Primary analyses were conducted on a microcomputer using SYSTAT (Evanston, IL).

## Results

### Risk Group Characteristics at Screening

Risk group comparisons are given in Table 1. The groups were comparable in anthropometric characteristics, although HiRsk participants were modestly heavier.

Average BPs taken over 15 min during the screenings showed the expected elevations in both systolic and diastolic BPs among HiRsk men,  $F_s(1,40) = 39/9.6$ ,  $p_s = .00005/.004$ . The average systolic BPs for the HiRsk group would place them at approximately the 90th percentile on Screening 1 and the 80th on Screening 2 using age group norms (National Institutes of Health, 1980). Among LoRsk men, the comparable percentiles are the 40th and 25th percentiles. The HiRsk group may be described as having high normal BPs and the LoRsk group as having low normal BPs.

Although BPs declined from the first to second screening,  $F_s(1,40) = 24/18$ ,  $p_s < .0001$ , the group difference was significant on both visits (+18/+10 mmHg,  $p_s < .001/.01$ , on Screening 1; +15/+7 mmHg,  $p_s < .001/.05$ , on Screening 2). There were greater reductions from the first to the second day in the HiRsk group (7/5 mmHg) than in the LoRsk group (4/2 mmHg).<sup>1</sup>

### Group Differences on Test Days

The cardiovascular and mood data are shown in Figure 1 and Table 2. Rest day values are shown as solid markers. The main ANOVAs showed that HiRsk participants had significantly elevated systolic and diastolic BPs,  $F_s(1,40) = 60/22$ ,  $p_s < .00001$ , accompanied by an elevated vascular resistance,  $F(1,40) = 6.63$ ,  $p = .014$ , based on main effects of group. The groups were not different in HR or CO,  $F_s(1,40) < 1.0$ , and no differences were found for reports of moods states,  $F_s(1,40) \leq 2.0$ ,  $p_s > .16$ . There were no interactions of group with days, periods, or Days  $\times$  Periods for any variable. Based on these results, further examination of group differences in BP and vascular resistance was conducted for each day.

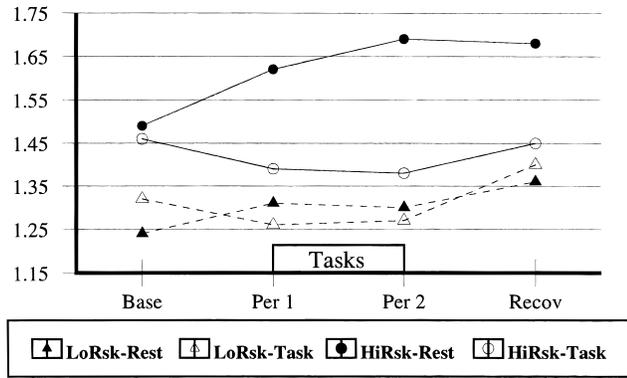
### Risk Groups on Rest Day

Unless otherwise noted, the results are based on the simple Groups  $\times$  Periods interactions for each day of testing.

Rest day systolic and diastolic BPs were elevated in HiRsk versus LoRsk men during the entire 180 min of observations, 124/70 mmHg versus 109/61 mmHg respectively,  $F_s(1,80) = 56/21$ ,  $p_s < .00001/.0001$ , confirming their screenings. BPs were stable over each observation period for each group, as indicated by nonsignificant periods effects,  $F_s(3,38) = 0.28/1.26$ , and by nonsignificant Group  $\times$  Periods interactions,  $F_s(3,38) = 0.10/1.11$ .

Vascular resistance levels showed a significant elevation among HiRsk men versus the LoRsk men on the rest day, as indicated by

<sup>1</sup> The Group  $\times$  Day interactions indicated a trend toward a greater reduction in diastolic BP among the HiRsk men,  $F(1,40) = 3.23$ ,  $p = .08$ , perhaps reflecting a response to the novel screening environment on Session 1.



**Figure 1.** Vascular resistance ( $\text{dyne} \cdot \text{s} \cdot \text{cm} \cdot 10^{-8}$ ) for 60 min of rest before onset of tasks (Base), the first and second 30-min periods during the tasks (Per 1, Per 2), and the 60 min of posttask rest (Recov). Rest day data are shown at comparable periods.

**Table 2.** Blood Pressure and Hemodynamic Variables

	LoRsk		HiRsk	
	Rest	Task	Rest	Task
Systolic blood pressure (mmHg)				
BSE	109 (1.5)	110 (1.4)	124 (1.5)	123 (1.4)
T1	109 (1.6)	118 (1.8)	123 (1.6)	131 (1.8)
T2	109 (1.5)	118 (1.9)	124 (1.6)	132 (1.9)
REC	109 (1.3)	111 (1.3)	124 (1.3)	124 (1.3)
Diastolic blood pressure (mmHg)				
BSE	61 (1.3)	61 (1.4)	69 (1.3)	70 (1.4)
T1	61 (1.3)	66 (1.5)	70 (1.3)	74 (1.5)
T2	60 (1.6)	66 (1.5)	70 (1.6)	73 (1.5)
REC	62 (1.4)	61 (1.6)	71 (1.4)	69 (1.6)
Heart rate (bpm)				
BSE	62 (2.1)	63 (2.3)	60 (2.1)	60 (2.3)
T1	61 (2.0)	69 (2.7)	59 (2.0)	67 (2.7)
T2	59 (2.0)	68 (2.8)	59 (2.0)	65 (2.8)
REC	61 (2.0)	62 (2.3)	59 (2.0)	59 (2.3)
Cardiac output (L/min)				
BSE	5.2 (0.4)	5.0 (0.3)	5.4 (0.4)	5.2 (0.3)
T1	4.9 (0.4)	5.9 (0.4)	5.0 (0.4)	5.7 (0.4)
T2	4.9 (0.4)	5.7 (0.4)	4.9 (0.4)	5.7 (0.4)
REC	4.8 (0.3)	4.9 (0.3)	4.8 (0.3)	5.1 (0.3)
Vascular resistance ( $\text{dyne} \cdot \text{s} \cdot \text{cm} \cdot 10^{-8}$ )				
BSE	1.24 (1.0)	1.32 (0.8)	1.49 (1.0)	1.46 (0.8)
T1	1.31 (1.1)	1.26 (0.9)	1.62 (1.1)	1.39 (0.9)
T2	1.30 (1.2)	1.27 (0.8)	1.69 (1.2)	1.38 (0.8)
REC	1.36 (1.1)	1.40 (0.9)	1.68 (1.1)	1.45 (0.9)
Activation ratings (1–10 scale)				
BSE	3.6 (0.37)	3.6 (0.38)	3.9 (0.38)	4.2 (0.39)
T1	3.3 (0.34)	3.1 (0.35)	3.8 (0.35)	4.0 (0.36)
T2	3.5 (0.34)	6.4 (0.24)	3.9 (0.35)	6.5 (0.25)
REC	3.4 (0.35)	3.5 (0.33)	3.8 (0.36)	4.0 (0.34)
Distress ratings (1–10 scale)				
BSE	3.8 (0.19)	3.9 (0.20)	4.1 (0.20)	4.5 (0.21)
T1	2.8 (0.42)	2.9 (0.39)	3.2 (0.43)	3.8 (0.40)
T2	4.0 (0.21)	5.2 (0.28)	4.2 (0.21)	5.9 (0.28)
REC	3.0 (0.42)	3.2 (0.42)	3.3 (0.43)	3.7 (0.43)

Note: BSE = 60 min rest, T1 = 0–30 min rest or task, T2 = 30–60 min rest or task, REC = 60 min rest; entries show mean ( $\pm$ SEM);  $n = 21$  in each group.

a significant effect of group,  $F(1,80) = 5.60, p < .005$ . Although vascular resistance increased over time,  $F(3,38) = 10.70, p < .0001$ , the effect was similar for both groups, as indicated by a nonsignificant Group  $\times$  Period interaction,  $F(3,38) = 1.84$ . The resting data indicate that the cause of the elevated BPs in the HiRsk group was an elevated vascular resistance.

### Task Effects

The primary analyses based on the Groups  $\times$  Days  $\times$  Periods ANOVAs indicated that the tasks produced significant elevations in cardiovascular activity relative to comparable rest day times. A series of significant Days  $\times$  Periods interactions revealed task-related elevations in BPs,  $F_s(3,38) = 38/28, p_s < .00001/.00001$ , HRs,  $F(3,38) = 36, p < .00001$ , COs,  $F(3,38) = 25, p < .00001$ , and lower vascular resistance,  $F(3,38) = 8.43, p < .0005$ . The effortful engagement in the alternating tasks appears to have produced consistent elevations in CO in each 30-min task period.

Mood reports taken at the end of the tasks indicated substantial increases in activation and distress as indicated by significant Day  $\times$  Period interactions,  $F_s(3,38) > 17.3, p_s < .00001$ . These data indicate that the tasks were effective at producing symptoms of mild stress for their duration.

### Risk Groups During Tasks

The risk groups did not differ in their BP responses to the tasks. The Groups  $\times$  Periods simple interaction terms were nonsignificant,  $F_s(3,38) < 1.0/1.0$ . The groups also had similar changes in vascular resistance over periods on the task day,  $F_s(3,38) < 1.5$ , based on Group  $\times$  Period simple interactions. Posttask reports of activation and distress were similar for the groups,  $F_s(3,38) < 2.0$ .

### Cardiac and Vascular Contributions to Blood Pressure Within Groups<sup>2</sup>

To test the relative contributions of CO and vascular resistance to group BP levels, we conducted a regression analysis in which MAP variance was predicted using CO and vascular resistance, averaged across periods on each day. On the rest day, HiRsk arterial pressure was predicted by vascular resistance,  $t = 2.41, p < .03$ , but not by CO,  $t = 1.84, p > .08$ . Among LoRsk participants, both CO and vascular resistance contributed to variance in resting arterial pressures,  $t_s > 4.7, p < .001$ . On the task day, in both groups, CO and vascular resistance each contributed variance to the measurement of MAP,  $t_s > 2.65, p_s < .02$ .

<sup>2</sup> Based on inspection of the vascular resistance data and based on the elevated vascular resistance values in the HiRsk group, we conducted an exploratory analysis contrasting vascular resistances on the rest versus task days separately for LowRsk and HiRsk groups using the simple Days  $\times$  Periods interaction terms.

The LoRsks did not differ in vascular resistance between rest and task days and did not show differential variation across periods on either day, as indicated by a nonsignificant days effect,  $F(1,40) < .003$ , and Days  $\times$  Periods interaction,  $F(3,38) = 2.14, p > .10$ .

The HiRsk group members exhibited significantly higher vascular resistance on the rest day than on the task day, as indicated by a significant Days  $\times$  Periods simple interaction,  $F(3,38) = 7.21, p < .001$ , and a simple main effect of days,  $F(1,40) = 17.7, p < .00001$ . The simple main effect of periods for the HiRsk group on the rest day was significant,  $F(3,38) = 9.86, p < .0005$ , indicating higher levels of resistance over time. The comparable effect on the task day was nonsignificant,  $F(3,38) = 1.97, p > .10$ , indicating stable vascular resistance values among HiRsks across task periods.

## Discussion

The present study examined the hemodynamic inputs responsible for BP elevations in HiRsk men familiarized with the laboratory and exposed on separate days to extended rest and to rest plus nonaversive behavioral challenges. The HiRsk participants did not have elevated CO at either time. Instead, elevated BPs among HiRsk participants were supported by a raised vascular resistance. In addition, the BP responses to the tasks were not greater in the HiRsk group. This pattern of results also occurred in a previous study on HiRsk men using similar tasks (Marrero et al., 1997).

In view of the elevated vascular resistance among the HiRsk men at rest and the balanced combination of vascular resistance and CO contributions to raised BP during the tasks, task-related activation appears to shift the dominant vascular resistance pattern among HiRsk men to a pattern of both CO and vascular resistance. Given that the tasks were minimally threatening, the question arises as to whether HiRsk men would have presented a more cardiac-predominant pattern in the case of tasks that are novel, highly threatening, or aversive.

These results raise three related issues for the design and interpretation of studies of cardiovascular reactivity in hypertension risk. (a) The findings are consistent with the vascular resistance model of hypertension development. (b) The findings suggest that conditions of testing and familiarity with the laboratory may differentially affect hemodynamic patterns of HiRsk persons at rest and during stressor challenge. (c) The findings yield testable predictions for future research.

### Models of Hypertension

In evaluating models of hypertension etiology, comparing HiRsk and LoRsk normotensive individuals would seem to be a simple process of observation. However, this comparison has proven unexpectedly difficult due to selection criteria and conditions of measurement. The two strongest risk factors for hypertension are PH+ and elevated BP (Higgins, Keller, Metzner, Moore, & Ostrander, 1980). Assignment of PH+ persons to the HiRsk group without regard to their BP levels has not proven satisfactory, with inconsistent BP reactivity across studies in PH+ persons (cf. Muldoon, Terrell, Bunker, & Manuck, 1993). Relative to parental history, a modestly elevated BP is about twice as strong a predictor of future disease (Julius et al., 1990), with elevated systolic BP predicting 2.3 times the risk of low normal BP. The two together provide the best early estimate of future risk (Ohlsson & Henningsen, 1982; Paffenbarger, Thorne, & Wing, 1968; Thomas & Duszynski, 1982), and this classification has yielded consistent reactivity differences (al'Absi et al., 1995; Everson et al., 1992; Marrero et al., 1997). This dual-risk-factor approach may be useful in future studies of hypertension risk and behavioral stress.

### Conditions of Testing and Methods of Measurement

Elevated sympathetic activation in HiRsk persons may cause differential reactivity to threatening situations. In normotensive animals, Mason (1968) showed that stimulus novelty is a potent trigger of pituitary-adrenocortical activation. In humans, fear and threat of aversive stimulation lead to increased cardiac output and reduced vascular resistance (Lovallo et al., 1985; Sinha, Lovallo, & Parsons, 1992). The central nervous system activation of HiRsk and borderline hypertensive (BH) groups would have the effect of exaggerating these tendencies, causing a range of responses as a result of the individual's psychological characteristics in combination with putative systemic effects associated with hypertension development. These signs would diminish with familiarity and

reduced sense of threat, thus unmasking the underlying hypertension-related response tendencies. Such a novelty effect was observed in endocrine responses of persons with BH, who had elevated resting cortisol levels on Day 1 in the laboratory but normal values on Days 3–4 (al'Absi & Lovallo, 1993).

*Laboratory studies.* Studies of reactivity in hypertension risk are often based on single exposures to the laboratory, short rest periods, and brief, unfamiliar tasks. Such conditions favor greater cardiac reactivity in BH or PH+ persons (Carroll, Harris, & Cross, 1991; Sausen, Lovallo, & Wilson, 1991; Sherwood et al., 1995; Trieber et al., 1993). In contrast, elevated vascular resistance was found in BH men adapted to the laboratory for 2–5 days (Sung, Lovallo, Teague, Pincomb, & Wilson, 1993) or in response to caffeine administration, a vasoactive stimulus (Pincomb et al., 1996). HiRsk volunteers had elevated HR and BP responses to a novel mental arithmetic task on their first laboratory visit (al'Absi et al., 1995), and they exhibited a "white coat" effect indexed by a significant decline in BP from simulated manual readings to a longer series of automated readings (Bernardy, Everson, al'Absi, Schott, & Lovallo, 1995). The present study involved no explicit threat and participants were well adapted to the laboratory, potentially diminishing cardiac reactions and leaving tonic vascular resistance increases in their place.

*Clinical studies.* The influence of novelty and threat may also affect clinical studies of hypertension development, and design issues in the major studies supporting the CO theory leave their conclusions in doubt. Two widely cited studies (Lund-Johansen, 1991; Weiss et al., 1978), using invasive methods to measure cardiac output, have reported that BH persons had elevated resting COs with normal peripheral resistances on initial evaluation, followed by a shift to normal COs and elevated peripheral resistances on subsequent observations. These results were interpreted as demonstrating the natural course of essential hypertension development. However, measurement of CO using cardiac catheterization and indicator dilution techniques is anxiety provoking and anxiolytic medications are often used in diagnostic procedures, although not in these studies. The volunteers were likely to have been highly anxious, particularly on their first evaluation.

Interpretation of these studies is limited by (a) lack of parallel observations of LoRsk control subjects, allowing age factors to play an unknown role in the changing hemodynamic patterns; (b) the use of antihypertensive medications and a changing patient composition across 20 years in the Lund-Johansen (1991) study; (c) the elevated COs of BH persons on initial observation were metabolically appropriate, not metabolically excessive, as called for in the hyperkinetic model (Lund-Johansen, 1991); and (d) compared with CO, high vascular resistance at entry to the Lund-Johansen study was more prognostic of future hypertension and need for medications. Based on these considerations, it is difficult to conclude with confidence that these studies support the hyperkinetic model of hypertension development.

The participants in these studies may have become less anxious with repetition of the invasive procedures, diminishing cardiac activation and leaving enhanced vascular resistance as the remaining sign of a tonically elevated sympathetic activity. Age factors would have had a similar effect due to declining  $\beta$ -adrenergic receptor densities. The presence of normotensive longitudinal control groups would provide a valid test of both hypotheses.

In relation to the hyperkinetic model, studies show a more mixed pattern of hemodynamic activation (e.g., Julius, Schork, &

Schork, 1988), and a population-based study found elevated vascular resistance in BH persons based on noninvasive techniques (VanHooft, Grobbee, Waal-Manning, & Hofman, 1993).

### Future Studies

In view of the foregoing considerations, we suggest that the question of an elevated CO in hypertension development be expanded to include the conditions of testing. We then might ask: Do HiRsk persons have elevated COs and greater BP responses to stress, and if so, under what conditions of testing? The present findings, in view of the range of results reported by others, suggest that the pattern of hemodynamic activity at rest and in response to behavioral challenges may vary according to the emotional background

of the testing. Conditions favoring fight-flight reactions and evoking anxiety appear more likely to produce CO differences and greater BP reactions among unadapted HiRsk men.

This hypothesis is amenable to empirical test. One approach would be to examine hemodynamic characteristics of risk groups over successive visits to the laboratory with systematic threat and nonthreat challenges over these visits. This sort of investigation may help in understanding differences among studies by clarifying the effects of specific emotional states in high risk groups.

The present results suggest that increased sympathetic nervous system activity in HiRsk men may manifest itself as an elevation of vascular resistance under conditions of familiarity with the test environment and lack of novelty or threatening incentives.

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