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Abstract: Impaired recovery and plasma concentration of intercellular adhesion molecule-1 (sICAM-1) were both highlighted as a plausible and a more established markers of cardiovascular disease, respectively. Hemodynamic patterns during recovery and their link with circulating levels of sICAM-1 were examined as predictors of 24-hour blood pressure (ABP). Impedance cardiography measures and beat-to-beat BP were recorded in 45 healthy subjects during a 10-min baseline, four tasks, and four 10-min recovery periods. sICAM-1 levels at rest were determined by ELISA. ABP measures were obtained combining data from a work and an off day. Hierarchical regressions showed that patterns of compensatory changes in cardiac output and total peripheral resistance during recovery improved the prediction of ABP above and beyond resting and recovery BP, or reactivity hemodynamic patterns. Stress-induced recovery was essentially

vascular in nature and a more vascularprofile was associated with higher ABP and higher circulating levels of sICAM-1. The results suggest a link between recovery hemodynamics and cardiovascular risk.

*** Response to Reviewers**

May 13, 2007

MS: JA1361

Dear Dr. Brownley,

My colleagues and I greatly appreciate the time and effort that you and the reviewers have given to the review of our paper. We were delighted to be informed that the revised manuscript was found acceptable by the original reviewers and that you were open to reconsider your decision.

Here are our responses to the minor concerns of Reviewer 2.

1. The last sentence in section 2.5.1 (Handgrip exercise) has been rewritten as it was not clear. It now indicates that CV changes associated with this low-intensity exercise (30% of maximal grip intensity) are not mediated by SNS increases. As an isometric task, it elicits a vascular reaction.

2. The rumination task has been found related to both vascular and mixed vascular/cardiac patterns. We described it as characterized by a mixed vascular/cardiac reaction based on results from our previous study using the same paradigm (Ottaviani et al., 2006). We hope that section 2.5.4 is now more complete.

3. We did not examine contractility information (e.g., PEP) as a dimension of cardiac performance because the present paper specifically aims to address the physiological determinants of blood pressure following the hemodynamic profile model proposed by Gregg et al. (2005). We agree on the fact that the issue of underlying physiological determinants of blood pressure is also relevant to heart rate, based on the assumption that sympathetic and parasympathetic nervous system regulation underlies changes of the cardiovascular system. In fact, studies have shown that not only BP, but also heart rate level and variability should be considered with respect to risk for cardiovascular disease. Despite these considerations, we thought that the complexity of the study and the number of variables included in the analysis did not allow the introduction of heart rate-related variables. Therefore, we decided to keep the focus on the hemodynamic profile model and avoid overanalysis of the data and a manuscript that would be hard to follow.

We hope that you will find these minor changes satisfactory and that the paper will be acceptable for publication.

Thank you,

Yours sincerely,

Cristina Ottaviani

Vascular Profile, Delayed Recovery, Inflammatory Process, and Ambulatory Blood Pressure: Laboratory-to-Life Generalizability

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1. Introduction

The objective of this study is to capture the reasons why the hypothesis of stress reactivity as a risk factor for hypertension and cardiovascular disease has failed to fulfill its promise. Despite the vast literature, the additional risk accounted for by the cardiovascular stress response beyond blood pressure level is either small or non-existent (Schwartz et al., 2003). A major gap in reactivity-based researches is the failure to capture laboratory-to-life generalizability (Carroll et al., 2001). In line with the cautions expressed in a recent review about the limits of focusing on blood pressure (BP) change (Kamarck and Lovallo, 2003), there is now evidence that generalizability can be improved by considering hemodynamic profile and compensation deficit patterns as measures of stress response (Gregg et al., 2005; Ottaviani et al., 2006). The term hemodynamic profile describes the relationship between cardiac output (CO) and total peripheral resistance (TPR) in the homeostatic regulation of BP (Gregg et al., 1999). The same hemodynamic profile may differ in the extent to which TPR and CO compensate for each other, and failure to compensate (compensation deficit) appears to be a critical issue in the prediction of BP (Gregg et al., 2002). Specifically, we demonstrated that a) earlier methods for classifying individuals based on difference scores (task level minus baseline) largely failed to predict everyday life BP and b) hemodynamic response patterns during specific tasks could overcome the limitations of traditional BP reactivity in the prediction of ambulatory BP (Ottaviani et al., 2006).

A major consequence of the dominance of reactivity-based theories is the failure to examine duration of activation. Only prolonged or chronic activation can lead to the pathogenic state that eventually leads to organic disease (Brosschot et al., 2006). The goal of this study was to determine the contribution of cardiovascular recovery to the prediction everyday life BP. Specifically, we tried to determine if the increase in information obtained by considering hemodynamic patterns over traditional reactivity measures alone extends to recovery measures (Ottaviani et al., 2006).

The best method of measuring recovery has not been established (Linden et al., 1997). Cardiovascular reactivity and recovery from stress have been quantified by assessing the change from baseline, reducing the process to a single value and thereby losing potentially important information. In the present study, we refer to "traditional recovery" as these BP change scores. Empirically, we know that both reactivity and recovery are dynamic processes (Llabre et al., 2004). These considerations led us to base recovery measures on a model that takes into account the physiological, multiplicative relationship between CO and TPR in determining BP (CO x TPR = mean arterial pressure), instead of simple BP change scores. There is evidence that the underlying components of recovery BP are dynamic processes; while vascular responses are continuing to increase during a task, myocardial responses have already begun to recover. Kelsey and colleagues (2004) specifically demonstrated the tendency of myocardial reactivity to peak and adapt quickly during some stressors, whereas vascular reactivity increases throughout the stress period. If this pattern of findings extends to poststress recovery periods, vascular responders might be expected to show delayed recovery relative to myocardial responders (Kline et al., 2002). Furthermore, if different patterns of change in CO and TPR characterize recovery processes, we should expect that hemodynamic profile and compensation deficit patterns would be more informative than traditional BP recovery based on change scores in the prediction of ambulatory BP. We have found these measures to be superior to change scores (Ottaviani et al., 2006).

Despite the important findings mentioned above, studies in which recovery has been linked with cardiovascular disease risk or hypertension have focused only on BP (Borghi et al., 1986; Gering and Pickering, 1995; Stewart and France, 2001). Alternatively, Steptoe and Marmot (2005) found that an increase in BP over a 3-year period was predicted by impaired post-stress recovery and that the elevation in BP recorded during the recovery period was determined by vascular rather than cardiac responses. A similar pattern of transient increase in cardiac index and prolonged changes in TPR has been observed during extended mental stress testing (Ring et al., 2002). Given that ambulatory BP monitoring has been evaluated as a reliable method of testing laboratory-based

measures in real-life settings and as an established predictor of major cardiovascular events (Verdecchia et al., 2003), we investigated whether profiles formed on the basis of patterns of CO and TPR recovery to laboratory tasks relate more closely to ambulatory BP levels than simple BP recovery change scores.

Although the precise nature of the relationship between cardiovascular recovery and later hypertension development is currently unknown, studies have proposed that prolonged increasing levels of BP may stimulate a proinflammatory response and that endothelial inflammation may herald the changes in arterial wall that characterize the hypertensive state (Intengan and Schiffrin, 2001). Despite studies showing effects of incremental increases in BP levels and corresponding increases in sICAM-1 level (Rohde et al., 1999), the clinical relevance of the relationship between BP and vascular inflammation is still unclear, and it is not possible to conclude whether BP is stimulating heightened inflammation or whether inflammation is occurring before the development of hypertension. Another possibility is that these effects work in tandem in atherogenesis.

In a recent review, Pieper and Brosschot (2005) raised the issue that real life stress studies are not systematically reviewed from the prolonged activation perspective. Many previous experiments have demonstrated that the autonomic nervous system can react more rapidly than the HPA axis. Thus, it is likely that the autonomic activity induced by a stressor will have a rapid effect on peripheral immune functions (Mills et al., 2003). Isowa and colleagues (2004) predicted that an acute stress task would elicit prompt activation of the autonomic nervous system and that this system, in turn, would mediate the enhancement of innate inflammatory response. The inflammatory reaction is known to inhibit endothelial vasodilatatory, antithrombogenic, and antiarteriosclerotic functions, all of which play an important role in the pathophysiology of hypertension and cardiovascular diseases (Bhagat and Vallance, 1997).

ICAM-1 expression is increased during inflammatory processes and mediates adhesion and transmigration of leucocytes to the vascular endothelial wall (van de Stolpe and van der Saag, 1996). Although it is not a traditional Framingham risk factor (age, sex, SBP, total cholesterol,

HDL-cholesterol, diabetic status, smoking status, and left ventricular hypertrophy), circulating levels of sICAM-1 are elevated many years in advance of developed clinical coronary disease (Vita et al., 2004, Chae et al., 2001). Prospective data (Hwang et al., 1997; Ridker et al., 1998) demonstrate an 80% higher risk of future myocardial infarction for subjects in the highest quartile at study entry (sICAM-1>260 ng/mL), independently of the traditional cardiovascular risk factors mentioned above.

Given the limited evidence concerning the inflammatory correlates of hemodynamic recovery, the present study further aimed to investigate the potential mechanisms involved in the relationship between delayed recovery and sICAM as established risk factors for the development of cardiovascular diseases. Simultaneous assessment of hemodynamic and immune measures may further identify mechanisms linking hemodynamic responses to stress, inflammatory processes, and risk for illness.

2. Materials and Methods

2.1. Participants

Forty-five people employed full-time in a variety of jobs at UCLA (16 men and 29 women; mean age = 33.6 (7.5)) were recruited by announcements and screened by phone for psychiatric disorder, significant health problems, and use of drugs or medications that might affect cardiovascular functions or complicate interpretation of the ambulatory BP data (i.e., coronary heart disease, diabetes, use of antihypertensive drugs). Subjects with severe obesity (body mass index [BMI] > 32 kg/m^2) or a prior diagnosis of hypertension were excluded. Also excluded were postmenopausal women and women who were pregnant or lactating within the previous 12 months. Parents of each subject were contacted in order to obtain health information for placement of subjects into appropriate family history groups (two hypertensive parents, one hypertensive parent, normotensive parents). Subjects were excluded if parents' BP status was unclear or could not be

verified. The sample included approximately equal numbers of subjects with and without a positive family history of hypertension (n = 12, one hypertensive parent; n = 10, two hypertensive parents; n = 23, neither). Subjects were paid $50. The experimental protocol was approved by the UCLA Institutional Review Board.

2.2. Procedure

The study protocol consisted of two ambulatory sessions and one laboratory session. For each individual, the two 24-hr ambulatory session and sICAM-1 measures were obtained from participation in a prior study. Venous blood samples for the assessment of sICAM-1 were taken before the beginning of the first ambulatory session. The average time between the two studies was 14.9 (7.6) months. Before each of the two ambulatory BP sessions three casual readings were taken with a mercury column sphygmomanometer and they were repeated before the laboratory session, providing a total of twelve casual assessments. Correlations between the mean of the measurements taken at the two different times (ambulatory and laboratory) were significant for both casual SBP, r = .51, and DBP, r = .54. Elapsed time and change in BP were not significantly correlated.

2.3. Assessment of sICAM-1

Blood sample was drawn for sICAM-1 after the subject had rested for 20-min. sICAM-1 levels were determined in plasma using commercial ELISA (R&D Systems, Minneapolis, MN). The precision and sensitivity was as follows: intra-assay CV = 4.6%, inter-assay CV = 6.6%, sensitivity < 0.35 ng/ml (Mills et al., 2002). sICAM-1 level values were obtained for 44 out of 45 subjects.

2.4. Ambulatory sessions

Ambulatory monitoring occurred on two separate sessions, one work day and one off work day, with days being counterbalanced. The time between the two sessions was one week. The

ambulatory recorder Accutracker II (Suntech Medical Instruments, Raleigh, NC) was programmed to operate on a variable schedule three times per hour during waking hours and once per hour during sleep. Each time the instrument operated during waking hours, subjects were instructed to keep arms still and at their sides and to fill out a diary immediately after. Ambulatory data were first edited for artifacts based on Accutracker reading codes (insufficient electrocardiogram or Korotkoff sounds) and extreme values (> 200/120 or < 70/40 mm Hg). Editing was done entirely by set rules (Goldstein et al., 1992). Of the total 6438 readings, there were 1229 exclusions (19%), with a mean number of 27.3 (*SD* 8.5) exclusions out of 143.8 (*SD* 13.1) per subject. Classification of wake and sleep periods was based on diary entries and post-session reports. Mean values of wake and sleep SBP and DBP were obtained.

2.5. Laboratory session

Participants were informed of the following restrictions: no caffeine, alcohol, nicotine, or strenuous exercise for 2 hours prior to the appointment. The laboratory experimental protocol consisted of an initial 10-min baseline period, followed by three 2.5-min tasks and one 2-min task; each task separated by a 10-min resting period. The session ended with a 10-min resting period. The subject was sitting upright and still for the entire session. The order of tasks was counterbalanced across subjects. We chose tasks based on their ability to elicit unique patterns of reactivity.

2.5.1. Handgrip exercise

Subjects were asked to squeeze a hand dynamometer for 2 minutes at 30% of maximal voluntary grip strength level. This is a low intensity exercise in which the cardiovascular changes are mediated by parasympathetic withdrawal and not by increased sympathetic activity (Kluess et al., 2000). It is a standardized physical task characterized by increased heart rate and vascular reaction related to isometric muscle activity (e.g., Porro et al., 1995).

2.5.2. Mirror-tracing task

Subjects were requested to trace a pattern between the lines of a star-shaped figure without touching the sides of the star. The task requires tracing while looking in a mirror as a shield prevented participants from looking directly at either their hand or at the pattern to be traced. The trial was over when the subject returned to the starting point, followed by the placement of a new pattern and a new trial. The mirror task was included in the assessment as a standardized non-physical stressor, eliciting a vascular response (Kasprowicz et al., 1990).

2.5.3. Computerized logical-mathematical task

By choosing the related button on a PC, participants were asked to determine if the conclusion to a randomly generated syllogism (e.g., if *"a > b*" and *"b < c*" then "*a < c*?") was true or false. If an answer was entered within the time limit of 5 s, a window displaying "Correct answer!" or "Incorrect answer!" appeared; if an answer took too long, a window displaying "Too late!" appeared. The logical task is an example of task eliciting a predominant cardiac response (Ottaviani et al., 2006).

2.5.4. Rumination task

The task required participants to ruminate on causes and consequences of a recalled episode in which they felt intense anger or rage (i.e. experiencing or witnessing others receiving abusive or unfair treatment). After a stressful event, people may ruminate about their distress, perpetuating cardiovascular activation (Gerin et al., 2006). Several investigators have found that anger-related tasks tend to elicit a vascular pattern (e.g. Davis et al., 2000) or a mixed cardiac and vascular response (e.g. Neumann & Waldstein, 2001). On the assumption that social tasks may be more representative of daily life stressors, and on the basis of the mixed hemodynamic reactivity obtained

using the same paradigm (Ottaviani et al., 2006), the rumination task was chosen as an example of task characterised by a cardiac/vascular response.

2.5.5. Laboratory recording

Electrocardiographic and impedance cardiographic measures were obtained using two separate recording systems. A Minnesota Impedance Cardiograph measured the impedance signal. Four bands of disposable cardiograph electrode tape (Label Technologies, Inc.) were placed circumferentially around the neck, chest, and abdomen according to published guidelines (Sherwood et al., 1990). Measurements were taken to ensure that the electrodes were at the appropriate distance from one another. Each signal was continuously recorded in 30-s epochs during baseline, each stressor task, and recovery. The Cardiac Output Program (Bio-Impedance Technology, Chapel Hill, NC) acquired, stored, and processed the electrocardiographic (ECG) and impedance cardiographic signals via PC. Each epoch was manually checked to ensure accuracy of the event waveform scoring. The Cardiac Output Program computed CO as the product of stroke volume and heart rate for each epoch. ECG was monitored with a multitrace recorder (AcqKnowledge: Biopac System, Santa Barbara, CA). Disposable Ag–AgCl electrodes (ConMed Corp.) were affixed at standard thoracic monitor sites (right clavicle and precordial site V6). Beat-to-beat BP was measured non-invasively, using a Finapres Continuous NIBP Monitor. Continuous BP readings were obtained via a finger cuff attached to the third finger of the non-dominant hand. The Finapres has been shown to compare well with intra-arterial BP readings (Petersen et al., 1995). For each epoch, mean arterial pressure readings were entered into the Cardiac Output Program to compute TPR.

2.6. Hemodynamic profile and compensation deficit

The equation CO x TPR = MAP describes the physiological relationship between CO and TPR in determining BP. Following the computational method proposed by Gregg et al. (2002), it is

possible to obtain an additive function that addresses the concept of hemodynamic profile by taking logarithms on both sides of the equation: log COr + log TPRr = log MAPr. The term "r" in the equation refers to the ratio of task to baseline values for reactivity and to the ratio of resting to baseline for recovery. According to the equations described above, the failure to compensate is a critical issue in the prediction of BP. Gregg et al. (2002) were the first authors to distinguish unambiguously between the concept of hemodynamic profile and compensation deficit by taking into account the orthogonal relationship between these two parameters. The concept of compensation deficit was achieved by a 45° rotation of the two-dimensional space formed by the cardiac output and total peripheral resistance dimensions. Specifically, participants are described as more *vascular reactors* when the algebraic increase in log TPRr exceeds that in log COr, and more *myocardial reactors* when the algebraic increase in log COr exceeds that in log TPRr. Compensation deficit increases as the algebraic sum of the log COr and log TPRr values increase.

2.7. Data analysis

Analyses were performed using Systat 9.0 (Systat Software Inc., Richmond, California, USA). All data are expressed as means (SD). Differences at $p < .05$ were regarded as significant. Gender and family history were treated as categorical variables. SBP, DBP, CO, TPR, hemodynamic profile, compensation deficit and s-ICAM levels were treated as continuous variables. The term "reactivity" refers to the 2.5/2.0-min during each task, and the term "recovery" refers to the 10-min resting period after each task.

Family history differences were analyzed by t-tests.

Paired t-tests were performed on CO, TPR, SBP, and DBP to test the differences between baseline and recovery periods for each task.

Traditional BP recovery scores were determined by subtracting the mean level obtained during the 10-min baseline from the average BP level measured during the 10-min recovery period after each task.

One-group *t*-tests were used to test the difference from zero of hemodynamic profile and compensation deficit scores for each task and recovery period (Gregg et al., 2002).

Correlational analysis was used to examine associations between recovery hemodynamic profiles and a) reactivity hemodynamic profiles; b) traditional recovery SBP; c) traditional recovery DBP; d) levels of the circulating sICAM-1.

Regression models were computed to predict ambulatory BP (SBP and DBP during wake and sleep). As mean work and nonwork day ambulatory BP were not statistically different and highly intercorrelated, we averaged the means of each day. Gender, Baseline BP, Hemodynamic Profile, Compensation Deficit, and Hemodynamic Profile x Compensation Deficit served as predictors. Inasmuch as age, BMI, sICAM-1, and family history of hypertension were consistently non-significant in all of the preliminary analyses, these variables were not included as covariates in the analyses. To increase stability (Hinz et al., 2000) and avoid overanalysis of data due to the small sample size, regression models were computed on hemodynamic data aggregated across tasks.

The analyses aimed at comparing the estimated variance that reactivity hemodynamics vs. recovery hemodynamics accounted for in predicting ambulatory BP, when other relevant variables were controlled for. In each case, we first examined the effects of gender and BP baseline, the obvious frontline predictors.

Model 1: Gender, Baseline BP, and traditional Recovery were entered, then Hemodynamic Profile and Compensation Deficit during recovery were successively entered as predictors.

Model 2: Gender and Baseline BP were entered, followed first by Hemodynamic Profile and Compensation Deficit during reactivity, and second by Compensation Deficit during recovery.

Specifically, we tested the hypothesis that recovery hemodynamics provide an increase in information over that afforded by traditional recovery (Model 1) and reactivity hemodynamic measures (Model 2).

3. Results

3.1. Blood pressure, cardiac output and total peripheral resistance during recovery

Figure 1 shows mean levels of CO, TPR, SBP, and DBP during baseline, task, and recovery for each task, respectively. CO after tasks was not significantly different from baseline levels. TPR recovered to baseline level after the handgrip exercise but remained significantly higher after the mirror task ($t(44) = -3.80$, $p < .0001$), the logical task ($t(44) = -5.18$, $p < .0001$), and the rumination task ($t(44) = -5.08$, $p < .0001$). Reactivity was accompanied by increases in BP which remained significantly higher than baseline levels for SBP after the handgrip exercise ($t(44) = -3.61$, $p < .001$), SBP and DBP after the mirror task ($t(44) = -4.77$, $p < .0001$ and $t(44) = -3.63$, $p < .001$, respectively), SBP and DBP after the logical task ($t(44) = -7.48$, $p < .0001$) and $t(44) = -4.11$, $p < .0001$, respectively), SBP and DBP after the rumination task ($t(44) = -6.86$, $p < .0001$) and $t(44) = -4.29$, $p < .0001$, respectively). Only DBP after the handgrip exercise was not significantly different from baseline. Thus, it would appear that the elevations in BP observed during the recovery period were essentially due to vascular reactivity.

3.2. Recovery patterns of hemodynamic profile and compensation deficit

Unlike patterns of reactivity hemodynamics (Ottaviani et al., 2006), the recovery profile was consistently vascular for all stressors. Figure 2 shows the relationship between hemodynamic profile and compensation deficit scores for recovery data aggregated across tasks. Specifically, one-group t-tests for hemodynamic profile and compensation deficit indicated that a vascular profile was induced by the handgrip exercise ($t(44) = 3.62$, $p < .001$ and $t(44) = 3.65$, $p < .001$, respectively), the mirror task ($t(44) = 3.15$, $p < .005$ and $t(44) = 5.21$, $p < .0001$), the logical task ($t(44) = 3.83$, $p < .0001$ and $t(44) = 7.06$, $p < .0001$), and the rumination task ($t(44) = 3.58$, $p = .001$ and $t(44) = 6.41$, $p < .0001$). Irrespective of the particular stressor involved, whereas CO was restored to baseline levels, TPR during recovery remained elevated compared to baseline levels.

However, a significant correlation ($p < .01$) was found between reactivity profiles and recovery profiles: $r = .55$ for the handgrip exercise; $r = .65$ for the mirror task; $r = .73$ for the logical task; and $r = .74$ for the rumination task.

3.3. Recovery hemodynamic profiles and blood pressure

Pearson intercorrelations between recovery hemodynamic profile and change scores (SBP and DBP recovery levels minus baseline) indicated a significant ($p < .01$) relationship for hemodynamic patterns and a) DBP after the handgrip exercise ($r = .59$); b) SBP ($r = .62$) and DBP ($r = .73$) after the mirror task; c) DBP ($r = .59$) after the logical task; d) SBP ($r = .57$) and DBP ($r = .55$) after the rumination task. The relationship was not significant for SBP after the handgrip exercise and SBP after the logical task. Specifically, the more vascular the profile was after the tasks, the less SBP and DBP recovered. Consequently, vascular reactivity was the major determinant of the higher BP levels observed during the recovery period compared to baseline.

There were no significant differences in traditional BP recovery and in hemodynamic profile and compensation deficit during recovery between subjects with a positive or a negative family history of hypertension.

3.4. Inflammatory marker and profiles

A significant ($p < .05$) relationship was found for baseline sICAM-1 levels and reactivity hemodynamic profile a) during the handgrip exercise ($r = .44$); b) during the logical task ($r = .48$); c) during the rumination task ($r = .45$). Moreover, baseline sICAM-1 levels were significantly interrelated with recovery hemodynamics after all tasks ($r = .47$ after the handgrip exercise task; $r = .34$ after the mirror task; $r = .45$ after the logical task; $r = .36$ after the rumination task. In general, a more vascular profile consistently corresponded to higher circulating sICAM-1 levels (see Figure 3) but the correlation was not significant for sICAM-1 levels and reactivity hemodynamic profile during the mirror task ($p = .06$).

3.5. Recovery and generalizability to real life

In order to evaluate the role of age, BMI, sICAM-1, and family history of hypertension as possible confounders in the regression models, we first examined the relationship between these variables and ambulatory BP. Inasmuch as all of the preliminary analyses were consistently non-significant, age, BMI, sICAM-1, and family history of hypertension were not included as covariates in the regression analyses.

Table 1 shows the results of the hierarchical regressions for Model 1, which aimed to test the superiority of recovery hemodynamics (Hemodynamic Profile and Compensation Deficit) over traditional BP recovery. In all regression models, except for the prediction of DBP during wake, gender was a significant predictor with men manifesting the greater effects. When other relevant measures were controlled for, traditional SBP recovery accounted for 33% of the variance of SBP during wake. However, recovery hemodynamics improved the prediction of SBP during wake, accounting for an additional 10% of the variance. Specifically, compensation deficit was a significant predictor ($\beta = -.41$; $F\ (1, 45) = 5.67$; $p = .02$). With regard to ambulatory SBP during sleep, the model including gender, baseline SBP and traditional SBP recovery accounted for 33% of the variance, while hemodynamic profile and compensation deficit ($\beta = -.50$; $F\ (1, 45) = 11.89$; $p = .001$) improved the prediction accounting for an additional 20% of the variance, a total of 53%. In the regression model for the prediction of ambulatory DBP during wake, baseline DBP was a significant predictor. Compared to traditional DBP recovery, hemodynamic profile and compensation deficit ($\beta = -.57$; $F\ (1, 45) = 6.79$; $p = .01$) improved the prediction, accounting for an additional 6% of the variance. Considering ambulatory DBP during sleep, 39% of the variance could be accounted for by the model including gender, baseline DBP, and traditional DBP recovery. However, recovery hemodynamic accounted for an additional 10% of the variance, with compensation deficit being a significant predictor ($\beta = -.36$; $F\ (1, 45) = 4.02$; $p = .04$).

Model 2 (Table 2) aimed to test the hypothesis that recovery hemodynamics provide an

increase in information over that afforded by reactivity hemodynamic measures. When other relevant measures were controlled for, compensation deficit during recovery improved significantly the prediction ($\beta = -.49$; $F(1, 45) = 7.50$; $p = .009$) accounting for an additional 11% of the variance of SBP during wake compared to reactivity hemodynamics. The model including gender, baseline SBP, and reactivity hemodynamics accounted for 33% of the variance of ambulatory SBP during sleep. When compensation deficit during recovery was entered in the hierarchical regression analysis, the model accounted for 55% of the variance of SBP sleep, and it was a significant predictor ($\beta = -.71$; $F(1, 45) = 19.61$; $p < .0001$). Considering ambulatory DBP during wake, 30% of the variance could be accounted for by the model including gender, baseline DBP ($\beta = .61$; $F(1, 45) = 13.82$; $p = .001$), and reactivity hemodynamics. However, compensation deficit during recovery accounted for an additional 11% of the variance ($\beta = -.49$; $F(1, 45) = 7.19$; $p = .01$). With regard to ambulatory DBP during sleep, the model including gender, baseline DBP, and reactivity hemodynamics accounted for 41% of the variance and compensation deficit improved the prediction accounting for an additional 9% of the variance ($\beta = -.44$; $F(1, 45) = 6.60$; $p = .01$), a total of 50%.

Hierarchical regressions showed that recovery hemodynamics provide an increase in information over that afforded by traditional recovery (Model 1) and reactivity hemodynamic measures (Model 2).

4. Discussion

Modern conceptions hold that health is maintained through patterns of organized variability, rather than static levels, in the face of constantly changing environmental demands (see Thayer and Brosschot, 2005 for a review). A corollary of this view is that sustained recovery, when the initial effect of stressors has terminated, is associated with a lack of dynamic flexibility and has a cascade effect on the dynamic relationship among biological system elements (Brosschot et al., 2005).

In their review of theoretical and methodological issues in psychological stress reactivity and recovery research, Linden and colleagues (1997) assert that recovery measures should provide an increase in information over that afforded by reactivity measures alone. The rationale for this position is that the utility of recovery measures will be minimal if they supply only information already captured by reactivity measures. In agreement with Gregg and colleagues (1999) who demonstrated that recovery shares only approximately 40% of common variance in hemodynamic responses with the stressor periods, the present findings indicate that recovery provides important information not captured by cardiovascular reactivity measures, and hence may prove useful in the prediction of longitudinal changes in BP and hypertension. Few studies have investigated the generalizability of recovery measures to the natural environment. To date, individual differences in cardiovascular recovery have been used to predict the dichotomous outcome of hypertension versus normal BP up to 10 years in the future, but very rarely as a predictor of short term, variable changes in BP (Stewart and France, 2001). Rutledge and colleagues (2000) found that recovery added 3% to the prediction of ambulatory BP above that predicted by regression models including both baseline and reactivity values. When baseline, reactivity, and recovery scores were each entered into the equations, only baseline and recovery scores remained reliable predictors, with reactivity not explaining any additional variance.

In the present study, regression analyses were conducted to determine the unique contribution of cardiovascular reactivity, traditional BP recovery, and recovery hemodynamic patterns to the prediction of everyday life BP after adjustment for standard clinical predictors of BP (gender, initial resting BP). In line with increased reliability as a measure of the degree of data aggregation across measurements (Hinz et al., 2006), aggregation across the four tasks provided a good test of whether hemodynamic profile and compensation deficit were useful in predicting ambulatory BP. In general, the results emphasized the usefulness of applying the model proposed by Gregg and colleagues (2002) to the recovery period in the prediction of daily-life BP. Specifically, compensation deficit greatly improved the prediction of ambulatory BP during sleep and wake

periods compared to traditional BP recovery and reactivity hemodynamics. The present data extend what we previously found for reactivity periods on the additional informative value of compensatory hemodynamic changes and strengthen the concept that no single physiological measure can explain the complex mechanisms of BP regulation.

As a limitation, the sample size may not have been adequate in some of the comparisons. Even if temporal stability of ambulatory blood pressure has been demonstrated in a youth population (Harshfield et al., 1999), a second limitation of the present study relates to the time lag between ambulatory and laboratory session. Third, our sample was totally composed of healthy subjects. Some authors recently hypothesized that, since delayed recovery occurs in subjects at genetic risk for hypertension even before the corresponding changes in reactivity or adaptation, these impairments may be among the earliest precursors of the development of essential hypertension in the population (Schneider et al., 2003). The present study failed to show a family history effect for recovery patterns. A possible explanation is related to the use of two instead of three groups to differentiate between positive and negative parental hypertension history, a method which is due to sample size limitations, although contrary to Manuck's recommendation (1996). To confirm this hypothesis, family history of hypertension was found to be a primary predictor of ambulatory BP when a larger sample size allowed us to discern differences between individuals with two hypertensive parents and those with one hypertensive parent (Goldstein et al., 2006).

Another possible limitation of the present study is that 10 minutes may not represent a sustained recovery period. Steptoe and colleagues (2006) recently highlighted that some biological stress processes may take longer to emerge and employed a 45-minute stress recovery period.

According to Gregg and colleagues (1999), hemodynamic profile during recovery involved primarily vascular responding, regardless of whether the task itself required active or passive coping. Given that laboratory tasks are supposed to be representations of naturally occurring active and passive stressors, present findings suggest that vascular responding may characterize recovery from stress in general, irrespective of the particular stressor involved. Moreover, we found that a

more vascular profile after the stressor corresponded to greater impairments as shown in higher BP recovery levels compared to baseline. This is of particular interest in light of evidence that hypertension is characterized by both elevated TPR and delayed recovery (Julius et al., 1983; Schuler and O'Brien, 1997). To our knowledge, these two factors have never been linked together in determining the course of cardiovascular disease. However, since stress-induced recovery seems essentially vascular in nature and a more delayed recovery is characterized by a more vascular profile, the present study offers potential insights for future studies on recovery hemodynamics and pathogenesis.

Folkow (2004) hypothesized that repeated episodes of stress over time cause changes in the wall-to-lumen ratio of arterioles, ultimately eventuating in a fixed increase in TPR and future hypertension. If elevations in BP in the presence of a stressor are damaging to the cardiovascular system, the damages may be amplified by other stress-associated elevations aside from the immediate presence of the stressor. Consequently, we may speculate that prolonged recovery plays a more direct role in promoting hypertension because of its association with increases in TPR.

In addition, we found that a more vascular profile during recovery is associated with higher circulating sICAM-1 levels. Adhesion molecule regulated leukocyte-endothelial adhesion is a critical step in the basic inflammatory processes of atherosclerosis characteristic of hypertension. There are several potential mechanisms that may account for the observed relationship between BP and sICAM-1. Theoretically, a vascular environment characterized by increased endothelial ICAM-1 activation and expression could lead to increased leukocyte/endothelial adhesion supporting basic inflammatory processes (Krieglstein and Granger, 2001). Increased sICAM-1 expression has also been demonstrated by endothelial cells in spontaneously hypertensive rats compared with normotensive rats (Komatsu et al., 1997). Furthermore, recent data suggest that cumulative elevations of inflammation-sensitive plasma proteins may predict future increases in SBP (Engstrom et al., 2003).

Our data provide a link between slow recovery and a clearly established biomarker of poor vascular function and health. Endothelial activation and elevated ICAM-1 expression are associated with impaired nitric oxide production and thus impaired vasodilation (Witte et al., 2003).

To conclude, the present findings demonstrate that the hemodynamics of recovery from and reactivity to stress provide vital information about risk for hypertension as shown by improved prediction of ambulatory BP and greater laboratory-to-life generalizability. Replication with a larger sample size, a wider range of tasks, and a longer recovery period is needed to further clarify the mechanisms underlying delayed recovery, vascular profile, and inflammatory process in the pathogenesis of cardiovascular disorders.

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Table(s)

Table 1

Hierarchical Regression Analysis for the Prediction of Ambulatory Blood Pressure (Model 1). Traditional BP Recovery, Hemodynamic Profile (HP), and Compensation Deficit (CD) relate to aggregated data across tasks (N = 45).

	SBP during Wake					**SBP during Sleep**				
	B	*SE*	*β*	R^2	*VIF*	*B*	*SE*	*β*	R^2	*VIF*
Gender	-5.74	1.72	-.49	.30**	1.43	-8.09	2.41	-.46	.27**	1.37
Baseline SBP	0.07	0.10	.11	.32	1.47	-0.09	0.14	-.10	.28	1.39
Recovery SBP	0.23	0.18	.24	.33	1.49	-0.11	0.25	-.08	.33	1.49
Recovery HP	-13.71	29.70	.06	.35	1.54	-39.85	43.10	-.12	.39	1.64
Recovery CD	-149.48	62.76	-.41	.43*	1.75	-274.08	87.95	-.50	.53**	2.04
	DBP during Wake					**DBP during Sleep**				
	B	*SE*	*β*	R^2	*VIF*	*B*	*SE*	*β*	R^2	*VIF*
Gender	0.26	0.92	.04	.10	1.11	-2.96	0.69	-.54	.35**	1.54
Baseline DBP	0.24	0.07	.52	.29**	1.41	0.10	0.06	.24	.36	1.56
Recovery DBP	0.22	0.18	.25	.29	1.41	0.29	0.17	.36	.36	1.56
Recovery HP	20.85	18.49	.20	.29	1.41	-18.22	15.63	-.19	.39	1.64
Recovery CD	-93.97	36.06	-.57	.40*	1.67	-77.25	32.73	-.45	.49*	1.89

*$P < .05$.

**$P < .01$.

Table 2

Hierarchical Regression Analysis for the Prediction of Ambulatory Blood Pressure (Model 2).

Hemodynamic Profile (HP) and Compensation Deficit (CD) relate to aggregated data across tasks

	SBP during Wake					**SBP during Sleep**				
	B	*SE*	*β*	R^2	*VIF*	*B*	*SE*	*β*	R^2	*VIF*
Gender	-5.48	1.67	-.47	.30**	1.43	-8.15	2.25	-.46	.27**	1.37
Baseline SBP	0.06	0.10	.10	.32	1.47	-0.06	0.13	-.06	.28	1.38
Reactivity HP	-9.68	27.29	-.06	.33	1.49	-48.58	36.79	-.19	.32	1.47
Reactivity CD	98.85	72.94	.30	.33	1.49	205.86	98.33	.41	.33	1.49
Recovery CD	-180.80	66.01	-.49	.44**	1.78	-394.06	88.99	-.71	.55***	2.22
	DBP during Wake					**DBP during Sleep**				
	B	*SE*	*β*	R^2	*VIF*	*B*	*SE*	*β*	R^2	*VIF*
Gender	0.16	0.91	.03	.10	1.11	-2.54	0.76	-.46	.35**	1.54
Baseline DBP	0.28	0.08	.61	.29**	1.41	0.11	0.06	.25	.40	1.67
Reactivity HP	13.74	14.52	.16	.30	1.43	-11.99	12.26	-.15	.41	1.69
Reactivity CD	46.99	35.80	.28	.30	1.43	66.92	33.12	.43	.41	1.69
Recovery CD	-80.99	30.19	-.49	.41*	1.69	-75.79	29.49	-.44	.50*	2.00

*$P < .05$.

**$P < .01$.

***$P < .001$.

Figure(s)

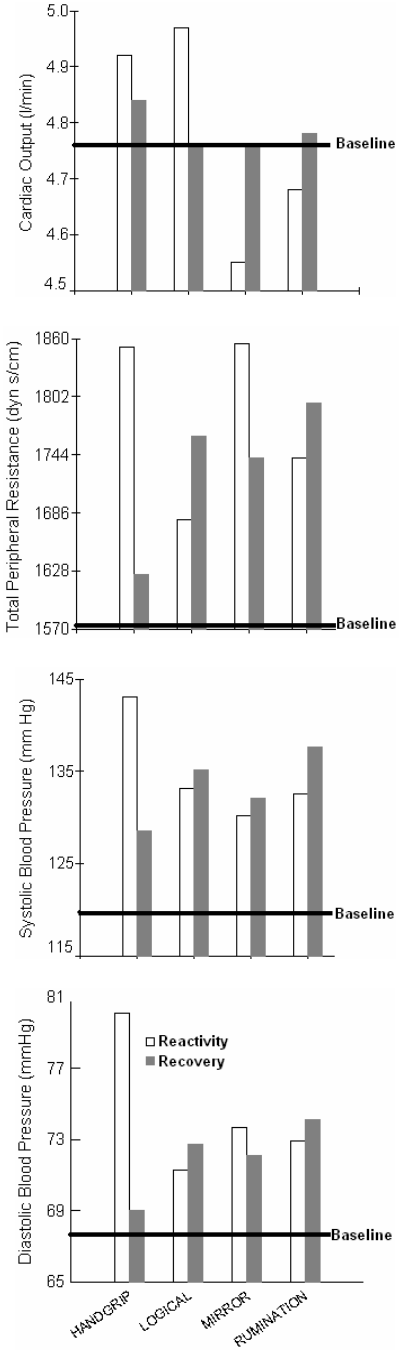

Fig. 1. Mean cardiac output, total peripheral resistance, systolic blood pressure, and diastolic blood pressure during reactivity and recovery periods (N = 45).

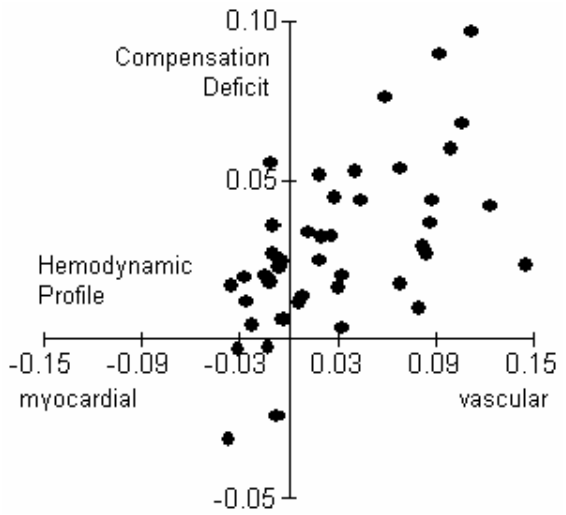

Fig. 2. Scatterplots for Hemodynamic Profile and Compensation Deficit for recovery data aggregated across tasks. A “more vascular” profile is associated with more positive values along the Hemodynamic Profile axis and a ”more myocardial” profile is associated with more negative values along the Hemodynamic Profile axis. A “higher deficit” in compensating is associated with more positive values on the Compensation Deficit axis and a “lower deficit” in compensating is associated with more negative values on the Compensation Deficit axis**.**

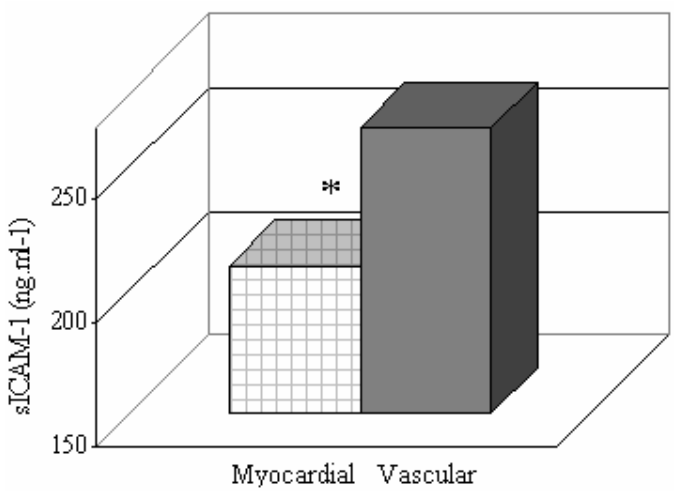

Fig. 3. Baseline sICAM-1 levels for myocardial (N = 18) and vascular (N = 27) profiles. Hemodynamic profiles obtained from data aggregated among tasks.

* = significance of the difference between the myocardial and the vascular profile; t = -2.97; p = .005.