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Reliability of hematocrit during rest and stress in healthy adults

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Abstract

Hematocrit has been implicated in the triggering of cardiovascular events and the development of cardiovascular disease. Studies have demonstrated the reliability of hematocrit at rest, however, data are lacking about hematocrit during repeated acute stress exposures. The current study assessed the reliability of hematocrit during rest and stress. Hematocrit was measured in two sessions during rest and in response to mental, cold and exercise stress in 84 healthy men and women. The stress tasks consistently elicited increases in hematocrit. Absolute levels of hematocrit were highly reliable between testing sessions. Changes in hematocrit with exercise stress were reliable whereas changes associated with mental and cold stress were not reliable between sessions. The findings indicate that hemoconcentration during brief mental and physical stress is more reliable for absolute levels than change scores. The reliability of stress-induced hemocontration may be improved by more provocative challenges and repeated sampling during stress.

Keywords: Hematocrit; Hemoconcentration; Reliability; Stress

1. Introduction

Mental, cold, and exercise stress have all been associated with the incident myocardial infarction (for review see Tofler and Muller, 2006). For example, deaths from ischemic heart disease were increased during a blizzard (Glass and Zack, 1979) whereas emotional upset and moderate physical activity were identified, first and second, respectively, as triggers by survivors of myocardial infarction (Tofler et al., 1990). However, the underlying mechanisms have yet to be established. One potential contributory mechanism linking stress to cardiovascular events is hemoconcentration, or an increased concentration of blood cells, proteins and lipids due to a decrease in the volume of plasma within the vascular compartment (Allen and Patterson, 1995). Hemoconcentration can be quantified by an increase in hematocrit (i.e., the percentage of red blood cells), which is a major determinant of blood viscosity (Dintenfass, 1985). Epidemiological studies have shown that rheological variables, such as hematocrit and blood viscosity, are associated with mortality from acute cardiovascular events, such myocardial infarction and stroke (Lowe et al., 1997; Woodward et al., 2003) and with increased risk of thrombosis and cardiac ischemia (Burge et al., 1975; Dintenfass, 1977; Isbister, 1987). Among patients with existing coronary artery disease, the hemoconcentration effects of acute stress may also affect parameters related both to myocardial supply (e.g., coronary thrombosis, decreased microcirculatory flow) and demand (e.g., increased work load of pumping high viscosity blood). Further, stress-induced hemoconcentration will increase the shear stress on the vessel wall, which at the site of a vulnerable atherosclerotic plaque could lead to plaque rupture and clot formation potentially resulting in myocardial ischemia (Corti et al., 2003; Falk et al., 1995; Worthley et al., 2001).

As yet there is only preliminary evidence that changes in hematocrit with stressful life events are associated with cardiovascular events. Kario and Matsuo (1995) reported that the increased incidence of events following the Hanshin-Awaji earthquake was associated with elevated hematocrit in the days after the earthquake compared to resting hematocrit determined a year or so earlier. Supporting evidence is provided by a recent

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study of patients with coronary artery disease showing that individuals who exhibited myocardial ischemia during a battery of stress tests (public speaking and mirror tracing) also showed greater concurrent increases in hematocrit (Bacon et al., 2006).

Hemoconcentration during mental stress has been consistently demonstrated in the laboratory. Evidence has accumulated to show that acute mental stress can reduce the volume of blood plasma (Patterson et al., 1995a) and increase the concentration of red blood cells (Bachen et al., 2002; de Boer et al., 2006; Jern et al., 1991, 1989; Mischler et al., 2005; Patterson et al., 1993, 1995a,b,c; Veldhuijzen van Zanten et al., 2002, 2004, 2005). Mental stress also influences other hemoconcentration-related factors, including colloid osmotic pressure (de Boer et al., 2007a,b) and blood and plasma density as well as blood and plasma viscosity (de Boer et al., 2007a,b; Patterson et al., 1995a, 1998; Muldoon et al., 1994; Steptoe et al., 2003). For example, using a time course design with blood measured every few minutes during rest, task and recovery, Patterson et al. (1995b) observed increases in blood and plasma density as well as a decrease in calculated plasma volume during stress. A recent time course study by de Boer et al. (2007b) showed that mental stress elicited increases in whole blood viscosity that were closely paralleled by increases in hematocrit. In sum, stress-induced hemoconcentration appears to be a fairly robust phenomenon.

The stability over time of stress-induced increases in hematocrit has yet to be formally investigated. The purpose of this study was to examine the reliability of hematocrit during stress. Many previous studies have expressed hemoconcentration as a percentage change in calculated plasma volume. Although this measure has the advantage of correcting for acute changes in red cell size (Dill and Costill, 1974), it has been criticized for exaggerating the extent of hemoconcentration (Harrison, 1985). While reductions in red cell size have been observed under extreme conditions, such as prolonged exercise, high temperatures and severe dehydration (Greenleaf et al., 1979; Harrison, 1985), red cell size is unchanged during mental stress (Patterson et al., 1995b; de Boer et al., unpublished observation), and, therefore, such correction seems unwarranted for most stressors. Based on previous research, red cell size is also likely to be unchanged by short duration low intensity exercise and temperature exposures used in the current study. Accordingly, hemoconcentration was indexed here by changes in the absolute levels of hematocrit.

The current sample included both male and female participants. The incidence of myocardial infarction is higher in men than women: age-standardized death rates from myocardial infarction were 74 and 34 per 100,000 in British men and women, respectively, in 1998 (World Health Organization, 2001). Further, circumstantial triggers for cardiac events are more commonly identified by men than women (Tofler et al., 1990; Culic et al., 2000). Several studies have reported sex differences in stress-induced hemoconcentration, with more pronounced hemoconcentration in men (Ross et al., 2001; Veldhuijzen van Zanten et al., 2004). It is possible that such sex differences might help explain why men have a higher incidence of myocardial infarction and appear to be more susceptible to stressful events reported to trigger acute cardiac events (see Tofler and Muller, 2006). Accordingly, the present study determined hematocrit in response to mental, cold, and exercise stress, and explored the reliability of stress-induced hemoconcentration in both men and women.

2. Method

2.1. Participants

Participants were 84 (50 men, 34 women) healthy adults with a mean age of 25 years (S.D. = 6) and a mean body mass index of 23 kg/m^2 (S.D. = 2). Participants were students and staff from the University of Birmingham who were recruited by advertisements placed on noticeboards around campus. None of the participants smoked or had a history of cardiovascular, pulmonary or immune disease. Individuals were excluded if they were currently taking medication, except for birth control. On average, participants exercised for 4 (S.D. = 3) h/week. They were asked to abstain from vigorous exercise and alcohol for 12 h and from caffeine for 1 h prior to testing. All participants gave informed consent and the study was approved by the local research ethics committee.

2.2. Measurements

Using separate venipunctures for each blood sample, blood was collected without stasis in a 4.5 ml tube containing potassium ethylenediaminetetraacetic acid (EDTA K3E 15%, 0.054 ml, BD Vacutainer, Meylan Cedex). Hematocrit (%) was determined using a cell counter (Hitechnicon Inc.) by the Department of Haematology Clinical Laboratory (C.P.A. accredited), University Hospital Birmingham NHS Trust. Brachial blood pressure was measured using a semi-automated auscultatory monitor (IBS-SD700, IBS Corp.). Heart rate was calculated from an electrocardiogram that was recorded continuously using spot electrodes in a chest configuration.

2.3. Stress tasks

2.3.1. Mental stress

Participants were required to add every number presented by tape player to the previously presented number and write down the answer. The 8-min task comprised four 2-min series of 50, 60, 75, and 100 single digit numbers at presentation rates of 2.4, 2.0, 1.6, and 1.2 s, respectively (Willemsen et al., 1998).

2.3.2. Cold pressor

Participants were required to keep their hand, up to the wrist-fold, immersed in 10 °C water for 4 min. Although the cold pressor test is traditionally conducted with lower water temperatures and shorter exposures, 10 °C water was chosen here to enable longer hand immersion while still eliciting a pressor response (Willemsen et al., 1998).

2.3.3. Exercise

Participants were instructed to pedal on a cycle ergometer (Monark, 668) at a workload of 50 W for 8 min.

2.4. Procedure

Participants attended two morning testing sessions that were scheduled 4 weeks apart. Each session consisted of a 30-min preparation and relaxation period, a 10-min baseline rest period, and three task periods separated by 10-min rest periods. Participants sat throughout. A blood sample was taken from a vein at the antecubital fossa to familiarize participants. Blood pressure measurements were initiated at the start of minutes 1, 5, and 9 of each rest period. A blood sample was obtained at the end of baseline. Participants then performed the three tasks with a 10-min formal rest period between tasks. The order of mental stress and cold pressor was counterbalanced but exercise was always

performed last. Blood pressure measurements were initiated at the start of minutes 1, 4, and 7 during mental stress and exercise but at the start of minutes 1 and 3 during the cold pressor. A blood sample was taken at the end of each task. An electrocardiogram was recorded continuously throughout.

2.5. Data reduction and analysis

Cardiovascular activity was reduced, for each parameter, to one value representing rest and one value representing each task. The 1-min averages for heart rate were averaged over minutes 6–10 and blood pressures were averaged across the second and third measurements of the rest periods preceding each task, and these were then averaged to yield overall resting values. No differences in cardiovascular function among the rest periods were detected. For the tasks, the 1-min averages for heart rate were averaged across the entire task period and all systolic and diastolic blood pressure measurements for each task were averaged. A series of 2 Sex (male, female) × 2 Session (first, second) × 4 Condition (rest, mental stress, cold pressor, exercise) repeated measures analyses of variance using the multivariate method (MANOVAs) were performed on hematocrit, heart rate, systolic blood pressure and diastolic blood pressure. Significant interaction effects were explored by comparing absolute change scores (change score = task value − rest value) using analysis of variance, with sex as a between-subjects factor and session as a within-subjects factor where appropriate. To assess test–retest reliability, a series of Pearson product-moment correlations and intra-class correlations were performed on the absolute levels of hematocrit for each condition in the first and second sessions as well as the respective residualized and absolute change scores for each task. Finally, correlations examined the consistency of changes in hematocrit among tasks within each session. Eta-squared is reported for effect size.

3. Results

3.1. Hematocrit and cardiovascular activity during rest and stress

Analyses were undertaken to characterize the effects of the stress tasks on rheological and hemodynamic function. It was expected that hematocrit, heart rate and systolic blood pressure would increase with each stress task. The 2 Sex × 2 Session × 4 Condition MANOVA yielded a condition main effect for hematocrit, $F(3, 80) = 62.33$, $p < .001$, $\eta^2 = .70$; Newman–Keuls post hoc comparisons indicated that hematocrit (%) was higher for exercise ($M = 41.1$, S.E. = 0.3) than mental stress ($M = 40.6$, S.E. = 0.3), higher for mental stress than cold pressor ($M = 40.4$, S.E. = 0.3), and higher for cold pressor than rest ($M = 40.0$, S.E. = 0.2). A main effect for sex, $F(1, 82) = 121.08$, $p < .001$, $\eta^2 = .60$, confirmed that hematocrit was over 6% higher in men than women. A sex × condition interaction effect, $F(3, 80) = 3.50$, $p < .02$, $\eta^2 = .12$, indicated that exercise elicited larger increases in hematocrit in women ($M = 1.7$, S.E. = 0.2) than men ($M = 1.0$, S.E. = 0.1) whereas mental stress and cold pressor provoked comparable hemoconcentration in both sexes. There were no main or interaction effects for session.

MANOVA applied to heart rates (bpm) revealed a condition effect, $F(3, 80) = 260.35$, $p < .001$, $\eta^2 = .91$; Newman–Keuls post hoc comparisons revealed incrementally faster heart rates from rest ($M = 65$, S.E. = 1) to cold pressor ($M = 66$, S.E. = 1) to mental stress ($M = 77$, S.E. = 1) to exercise ($M = 101$, S.E. = 2). A small but significant session by condition interaction effect emerged for heart rate, $F(3, 80) = 7.63$, $p < .001$, $\eta^2 = .22$; which was driven by heart rate increasing above resting levels by two beats per minute more during mental stress in the first session ($M = 13$, S.E. = 1) than the second session ($M = 11$, S.E. = 1). A main effect for sex, $F(1, 82) = 24.91$, $p < .001$, $\eta^2 = .23$, confirmed that heart rates were over 10 beats/min faster in women than men. A sex × condition interaction effect, $F(3, 80) = 9.26$, $p < .001$, $\eta^2 = .26$, indicated that exercise elicited greater increases in heart rate in women ($M = 35$, S.E. = 1) than men ($M = 29$, S.E. = 2) whereas mental stress and cold pressor provoked similar cardiac effects in both sexes. There was no session main effect. The systolic blood pressure (mmHg) analyses revealed a main effect for condition, $F(3, 63) = 62.73$, $p < .001$, $\eta^2 = .75$, and an interaction effect for session by condition, $F(3, 63) = 4.68$, $p < .01$, $\eta^2 = .19$. Newman–Keuls post hoc comparisons showed that systolic pressure increased from rest ($M = 118$, S.E. = 1) to each task, and moreover that there were further increases from mental stress ($M = 123$, S.E. = 2) to cold pressor ($M = 129$, S.E. = 1) to exercise ($M = 144$, S.E. = 2). The interaction effect detected that the systolic blood pressure response was 4 mmHg greater during mental stress in the first session ($M = 7$, S.E. = 1) than the second session ($M = 3$, S.E. = 1). There was also a main effect for sex, $F(1, 65) = 27.96$, $p < .001$, $\eta^2 = .30$, with systolic blood pressure 12 mmHg higher in men than women. The diastolic blood pressure (mmHg) analyses revealed a main effect for condition, $F(3, 62) = 48.69$, $p < .001$, $\eta^2 = .70$. Newman–Keuls post hoc comparisons showed that diastolic blood pressure increased from rest ($M = 76$, S.E. = 1) to mental stress ($M = 80$, S.E. = 1), and from mental stress to cold pressor ($M = 85$, S.E. = 1), and, moreover, that diastolic blood pressure decreased from rest to exercise ($M = 70$, S.E. = 1). There was also a main effect for sex, $F(1, 64) = 5.04$, $p < .03$, $\eta^2 = .07$, with diastolic blood pressure 4 mmHg higher in men than women.

In sum, these analyses indicated that the stress tasks elicited the expected hematological (Allen and Patterson, 1995) and hemodynamic effects (Ring et al., 2000; Winzer et al., 1999). First, cold pressor, which was characterised by the smallest hemoconcentration, elicited large increases in both diastolic and systolic blood pressures with little change in heart rate. Second, mental arithmetic, which was characterized by a middle-sized increase in hematocrit, elicited modest increases in heart rate as well as both systolic and diastolic blood pressures. Finally, dynamic exercise, which was characterised by the greatest hemoconcentration, elicited large increases in both heart rate and systolic blood pressure combined with a slight reduction in diastolic blood pressure.

3.2. Inter-session reliability of hematocrit

Correlational analyses using Pearson product-moment correlations were performed to determine the inter-session reliability of the absolute levels of hematocrit as well hematocrit change scores. These analyses were performed on the whole sample as well as on male and female subsamples. In addition, intra-class correlations were calculated on the whole sample to assess inter-session reliability. It was expected that hematocrit would be reliable across sessions. Correlational

Table 1
Inter-session correlation coefficients (r) for men, women and combined for absolute levels of each condition as well as the task-induced absolute change scores and residualized change scores for hematocrit

Condition	Men ($N = 50$)	Women ($N = 34$)	Combined ($N = 84$)
Absolute levels			
Rest	.57***	.59***	.82*** [.82***]
Mental stress	.60***	.60***	.81*** [.81***]
Cold pressor	.60***	.63***	.82*** [.82***]
Exercise	.57***	.55***	.76*** [.76***]
Absolute change scores			
Mental stress	−.08	.24	.09 [.09]
Cold pressor	.08	.10	.09 [.09]
Exercise	.09	.29#	.22* [.22*]
Residualized change scores			
Mental stress	−.06	.26	.10 [.10]
Cold pressor	.10	.12	.11 [.11]
Exercise	.13	.30#	.21# [.20*]

Intra-class correlations are computed [in the brackets] for the combined sample only. *Note*: #$p < .10$, *$p < .05$, ***$p < .001$.

analyses on absolute levels of hematocrit measured in each session revealed significant test–retest reliability over 1 month for rest, mental stress, cold pressor and dynamic exercise for men, women and both sexes combined (see Table 1, top). In contrast, the analogous correlations on absolute and residualized change scores were generally not significant for either sex or combined, with the exception of changes during exercise which were modestly correlated between sessions for women and the entire sample (see Table 1, middle and bottom).

3.3. Inter-task consistency of stress-induced hemoconcentration

Pearson product–moment correlational analyses were performed to determine the inter-task reliability of task-induced changes in hematocrit. Again, these analyses were performed on the whole sample as well as on male and female subsamples. It was expected that stress-induced changes in hematocrit would be reliable among conditions with each testing session. Correlations on both the absolute and residualized change scores elicited by mental stress, cold pressor and exercise during each session revealed significant associations among reactivity scores with the exception of those comparing exercise-induced changes in women (see Table 2).

4. Discussion

The key findings of this study were threefold. First, hematocrit levels during stress (mental, cold, exercise) were reliably reproduced across a test–retest assessment period of up to 1 month. Second, the stress-induced changes in hematocrit were reliable for exercise stress but not mental stress or cold stress. Third, intra-individual changes in hematocrit were consistent across stress tasks. These data are compatible with the results of previous reactivity studies that have shown that absolute levels of cardiovascular activity are more highly correlated than reactivity scores over repeated testing sessions (e.g., McKinney et al., 1985; Willemsen et al., 1998). Range restriction effects (Howell, 1997) may help to explain why the coefficients were higher for exercise than mental stress or cold pressor: the mean (S.E.) hematocrit change scores were +1.3% (0.1), +0.6% (0.1) and +0.4% (0.1), respectively. Accordingly, more provocative tasks may be expected to improve the test–retest reliabilities of hemoconcentration effects associated with mental and cold stressors. Blood samples were collected immediately after each task had been completed, and therefore, it is possible that the slightly delayed timing of blood collection may have attenuated stress-induced hemoconcentration effects.

The reliability of hemoconcentration with acute stress exposures has implications for future research. Methodologically, studies examining stress-mediated changes in large

Table 2
Inter-task consistency (r) of hematocrit absolute and residualized change scores for each session

	Men ($N = 50$)		Women ($N = 34$)		Combined ($N = 84$)	
	Mental stress	Cold pressor	Mental stress	Cold pressor	Mental stress	Cold pressor
Absolute change scores						
Session 1						
Cold pressor	.54***		.34*		.46***	
Exercise	.39**	.51***	.09	.27	.29**	.43***
Session 2						
Cold pressor	.42**		.64***		.54***	
Exercise	.47***	.34*	.45**	.31#	.47***	.34***
Residualized change scores						
Session 1						
Cold pressor	.53***		.35*		.46***	
Exercise	.38**	.50***	.11	.28	.28**	.41***
Session 2						
Cold pressor	.40**		.63***		.52***	
Exercise	.47***	.34*	.46**	.31#	.45***	.32**

Note: #$p < .10$; *$p < .05$; **$p < .01$; ***$p < .001$.

molecules found in the blood (e.g., lipids, proteins) need to take into account the possibility of systemic fluid shifts and need to control for possible hemoconcentration effects. For example, stress-induced hemoconcentration has been shown to account fully for the changes in lipids during acute stress (Bacon et al., 2004; Muldoon et al., 1992; Patterson et al., 1993). Hemoconcentration effects can also account, at least partly, for stress-induced changes in lymphocytes (Bacon et al., 2004; Mischler et al., 2005; Marsland et al., 1997). However, hemoconcentration effects may go beyond this. For example, it is possible that research assessing acute changes in molecules associated with the clotting process (e.g., fibrinogen, platelet proteins) during acute stress may need to consider the possible effects of changes in plasma volume or blood volume since these substances do not passively pass through the vessel wall with the efflux of fluid.

The pathophysiological relevance of stress-induced hemoconcentration effects is illustrated by data suggesting that stress is involved in cardiovascular events (Hirsch, 1987; Yarnell et al., 1991). A possible causal role for stress in coronary thrombosis has been suggested, but not yet proven, although several lines of evidence point to effects of stress on hemostatic factors. By demonstrating stress-induced hemoconcentration effects in healthy individuals, it is possible that among patients with coronary artery disease, the hemoconcentration effects of acute stress might affect parameters related both to myocardial supply (e.g., coronary thrombosis, decreased microcirculatory flow) and demand (e.g., increased work load of pumping high viscosity blood). Further, the increase in shear stress associated with stress-induced hemoconcentration in patients with a vulnerable atherosclerotic plaque could lead to plaque rupture (Corti et al., 2003; Falk et al., 1995; Worthley et al., 2001). Studies are needed that address the possible relationship between acute stress-induced changes in these hemoconcentration factors and acute cardiovascular events.

A limitation of the current study was that only a single blood sample was collected for each rest and task condition. Given that reliability of measurement improves with the square root of the number of observations, increased sampling rates should improve the reliability of stress-induced changes in hematocrit. It is also possible that the reliability of stress-induced changes in hematocrit would have been improved by obtaining a resting blood sample immediately prior to each task. Only two time periods that were up to 4 weeks apart were examined, and therefore, the reliability of stress-induced hemoconcentration over multiple and longer periods needs to be investigated. Finally, the current study focused on stress-induced hemoconcentration in healthy young adults. Studies are needed that measure reliability in patient populations, such as individuals with hypertension or coronary artery disease. Several other suggestions for future studies of stress-hemoconcentration effects and their reliability can be offered. One suggestion is to assess stress-induced hemoconcentration under more naturalistic settings. The mental stressors that have been employed in most of the studies examining stress-induced hemoconcentration have been rather short in duration. However, stressors that are encountered in everyday life are often of much greater potency and longer duration than laboratory stressors. The degree of hemoconcentration as a result of potent naturalistic stressors may be even greater than that usually seen in the laboratory. Another area of future research concerns individual differences. It may be of interest to examine stress-induced hemoconcentration as an individual difference variable. As with other variables in reactivity studies, there is a wide range of individual responses in intravascular fluid shifts and changes in hematocrit. Although hemoconcentration has been consistently found in stress studies, it is clear that some individuals show little or no hemoconcentration, and a relatively small proportion of people may even show a decreased hematocrit.

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