Acute Cholesterol Responses to Mental Stress and Change in Posture

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• ***Background.***—**Serum lipid levels vary widely within individuals, but the causes of these fluctuations are poorly understood. One area of research concerns elevations in cholesterol concentration in response to emotional stress. In a laboratory-based experiment, we compared the effects of acute mental stress and postural change (standing) on serum cholesterol concentration. In addition, plasma volume was indirectly monitored to determine whether cholesterol changes with mental stress, if present, were a function of hemoconcentration.**

Methods.—**Twenty-six men attended two laboratory sessions, each consisting of baseline (30 minutes), task (20 minutes), and recovery (30 minutes) periods. Subjects rested in the supine position during the baseline and recovery periods. During the task period of one session, subjects performed a mental task (Stroop test and mental arithmetic); during the other session, the subjects stood for the task period.**

Results.—**Both mental stress and standing elicited significant elevations in heart rate, blood pressure, and plasma catecholamine concentrations, relative to the baseline and recovery periods. Both the mental and orthostatic tasks also significantly increased serum cholesterol concentration (by 0.10 and 0.57 mmol/L [3.7 and 21.9 mg/dL], respectively), as well as hemoglobin level and hematocrit. Cholesterol elevations with standing were reversible, while those resulting from mental stress persisted through the recovery period. When values were corrected for concomitant hemoconcentration, no net change in serum cholesterol level occurred during either task.**

Conclusions.—**Acute mental stress can produce rapid elevations in serum cholesterol concentration. It can also increase hemoglobin concentration and hematocrit (ie, reduce plasma volume). Therefore, increases in serum cholesterol level after acute mental stress are analogous to those with standing and may reflect hemoconcentration rather than altered lipoprotein metabolism.**

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While risk of vascular disease varies with serum cholesterol concentration, lipid levels are not stable, and recent reports describe day-to-day variability of 10% to 20% within individuals.[1,2] In addition to presenting clinical problems in patient classification and treatment, these fluctuations are poorly understood mechanistically because they are not attributable to measurement error or change in diet. Indeed, in comparison with the wealth of data on the epidemiology of cholesterol, little is known about factors responsible for within-individual serum lipid fluctuations.

Psychological stress has been reported to raise cholesterol levels and may partially account for within-individual lipid variability. Furthermore, it has been proposed that such stress-induced elevations in serum lipid levels mediate the association between emotional stress and heart disease.[3,4] However, the hypothesized effects of stress on lipids is based largely on uncontrolled observations.[3,5-8]

In the only experimental evidence that emotional stress affects serum cholesterol concentrations, Stoney et al[4,9] described significant elevations within several minutes of exposure to a common laboratory stressor. The rapidity of these changes is striking because it appears to preclude altered lipoprotein metabolism.

Alternatively, stress could raise cholesterol levels as a function of hemoconcentration. The process of hemoconcentration refers to rapid and often transient filtration of fluid out of the intravascular space, resulting in the passive increase in concentration of all nondiffusible constituents (eg, all plasma proteins and blood cells). According to this "hemoconcentration hypothesis," mental stress reduces blood volume and raises cholesterol concentration without necessarily affecting lipoprotein metabolism. This theory is consistent with recent population-based data showing that cholesterol level elevation after the threat of job loss correlates with rise in hemoglobin concentration.[8]

In comparison with the uncertainties regarding the effects of stress on serum lipid levels and the mechanism underlying any such effect, postural manipulations (eg, standing) raise serum lipid levels in a manner that is both well characterized and widely understood to reflect hemoconcentration. Although often not considered when blood samples are obtained clinically, total cholesterol level rises by 9% to 25% within 30 minutes with movement from the supine to the erect posture.[10-12] These changes in serum lipid concentrations are completely reversible and proportional to changes in other nondiffusible blood constituents (eg, hemoglobin and albumin).[11] Comparable experimental data concerning the possible effects of mental stress on serum lipid levels are not available. Therefore, in this investigation,

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we sought to determine whether mental stress acutely elevates serum cholesterol concentration in a controlled, laboratory setting. Our second objective was to determine whether any changes observed reverse on termination of the stressor, and whether they are attributable to hemoconcentration. For purposes of comparison, the effects of postural change were measured in the same subjects on a separate occasion.

SUBJECTS AND METHODS

Subjects

Twenty-six men recruited from poster advertisements at the University of Pittsburgh (Pa) served as subjects for this experiment. All subjects were healthy, normotensive, and nonobese (body mass index, <30) and ranged in age from 18 to 30 years. In adherence with University of Pittsburgh Investigational Review Board specifications, experimental procedures were explained to each subject and informed consent was obtained. All subjects were paid for their participation.

Procedures

Each subject attended two laboratory sessions, one for completion of the stressful mental task and the other for postural manipulation. The two sessions were procedurally similar. Each lasted 90 minutes and consisted of a 30-minute baseline, followed by a 20-minute task period (for either the postural manipulation or mental stress), and finally a 30-minute recovery period. The duration for the baseline period was selected because fluid filtration after change in posture is completed within 30 minutes[10,13]; hence, any change in the concentration of a blood constituent observed later in the laboratory session is attributable to the experimental task. The sessions were scheduled 1 week apart and were counterbalanced for order of task presentation. All subjects fasted overnight and abstained from caffeine and smoking for 12 hours before the experiment. No subject reported using any medication for at least 2 days before each session.

On arrival at the laboratory, subjects assumed the supine position in a reclined chair with legs elevated to within 15 cm of the level of the heart. This position was maintained throughout both laboratory sessions, except during the orthostatic stimulus. An opaque screen was erected to block the subject's vision of his right arm and the blood-drawing apparatus. An 18-gauge intravenous catheter was then inserted aseptically into a vein in the antecubital fossa and connected to heparinized sterile tubing leading to an adjacent peristaltic pump and fraction collector. Subsequently, blood samples for measurement of total cholesterol, hemoglobin, hematocrit, and catecholamine levels were obtained periodically without the subject's awareness. An inflatable cuff was applied to the left arm and connected to a vital-sign monitor (Dinamap 8100, Critikon, Tampa, Fla) for measurement of blood pressure and pulse rate. Subjects then rested for the 30-minute baseline period.

Mental Stress and Postural Manipulation

The mental stress consisted of two frustrating cognitive tasks: a modified Stroop color-word interference test[14,15] and mental arithmetic. During the 20-minute mental stress, these two computerized tasks were presented in alternating 5-minute bouts. Each subject responded under pressure of time on a keypad positioned under his left hand. The mental arithmetic consisted of one- to three-digit addition and subtraction problems. During the Stroop task, one of four color words printed in an incongruent color (eg, "RED" printed in green) appeared in the center of the screen. Subjects were instructed to identify the color of the print (not the color name) by pressing one of the keys corresponding to the four color names appearing at the base of the computer screen, again printed in discrepant colors. To increase task difficulty, a computerized voice synthesizer provided distracting random test responses. Monetary incentives for performance (up to $20) were provided. To maintain task difficulty and adjust for individual differences in ability, the number of digits in each arithmetic problem and the time permitted for each Stroop task response were automatically adjusted according to the subject's performance (eg, when a subject responded correctly to several consecutive Stroop stimuli in the time allowed, task difficulty increased). As a result of these procedures, all subjects attained a performance level of approximately 60% correct responses.

For the postural manipulation, each subject rose from the supine to the standing position at the end of the baseline period, maintained an erect posture for the 20-minute task period, and then resumed the supine position for the 30-minute recovery period. To limit venous pooling in the legs and associated orthostatic hypotension, subjects were instructed to shift their weight and periodically flex their legs while standing.

Dependent Measures

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured twice at the end of the baseline and recovery periods and every 2 minutes during the mental and orthostatic task periods. Blood samples for measurement of total serum cholesterol, norepinephrine, epinephrine, hemoglobin, and hematocrit levels were obtained over 1 minute at the end of the baseline and recovery periods and during the third and 18th minutes of each task period.

Blood Assays

Total serum cholesterol concentrations were determined enzymatically[16] by means of a bichromatic autoanalyzer in the Heinz Nutrition Lipid Laboratory of the University of Pittsburgh, which has met the accuracy and precision standards of the Centers for Disease Control since 1982. Hematocrit and hemoglobin concentrations were employed as indexes of hemoconcentration and were determined with an automatice cell counter (STKR Coulter Counter, Goulter Electroniks Inc, Hialeah, Fla). Hematocrits were calculated automatically from the red blood cell concentration and the impedance-determined mean corpuscular volume; hemoglobin concentrations were measured by the cyanomethemoglobin method.

Blood samples for catecholamines were immediately anticoagulated with edetic acid (EDTA), chilled, and centrifuged; plasma was then removed and frozen at −80°C until analysis. Epinephrine and norepinephrine concentrations were determined after extraction with alumina by high-performance liquid chromatography with electrochemical detection with the use of a phase II, reverse-phase, 3-μm column. Peak catecholamine heights were measured automatically by computer.

Data Analyses

Three sets of analyses were conducted to determine the following: (1) the pattern of cardiovascular and catecholamine responses elicited by the two tasks; (2) the effects of these tasks on serum cholesterol concentration, blood hemoglobin concentration, and hematocrit; and (3) insofar as cholesterol level changed, the extent to which such change was a function of hemoconcentration. The HR, SBP, and DBP data were first reduced by calculating a mean of all values obtained during the last 4 minutes of the baseline and recovery periods and by averaging measures obtained over successive 4-minute intervals during the two task periods. Repeated-measures analyses of variance were then conducted on these mean values, as well as on plasma measurements of epinephrine and norepinephrine. Since data were incomplete for six subjects during the orthostatic task (due to fainting, nonattendance, and vein collapse), analyses were conducted separately for the orthostatic and mental stress manipulations. Each analysis of variance involved one between-subject factor (task order, ie, order 1, order 2) and one within-subject factor (period of measurement). For HR and blood pressure, there were seven measurement periods: baseline; five 4-minute intervals ending at minutes 4, 8, 12, 16, and 20 of the task periods; and recovery. For plasma catecholamines, analyses included four periods of measurement: baseline, minutes 3 and 18 of the tasks, and recovery.

In an analogous fashion, repeated-measures analyses of variance

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Mean (±SD) Levels of Heart Rate, Blood Pressure, and Plasma Catecholamines for Baseline, Task, and Recovery Periods During Stress and Orthostatic Manipulations*

	Baseline	Task Period T1	T2	T3	T4	T5	Recovery
Mental Stress (n=26)							
HR, beats/min	54.9±7.4	69.8±13.1	67.2±11.7	67.8±12.1	67.2±10.4	64.1±10.0	55.8±7.2
Blood pressure, mm Hg							
Systolic	114.9±5.8	124.0±8.7	125.5±8.2	124.3±8.0	126.1±8.4	123.3±8.1	117.0±7.6
Diastolic	60.6±9.0	66.1±10.6	67.0±9.8	66.5±9.3	65.8±9.1	64.2±9.9	61.3±8.4
NE, nmol/L	1.40±0.65	1.46±0.59	. . .	. . .	. . .	1.44±0.57	1.41±0.56
E, pmol/L	125±56	203±153	. . .	. . .	. . .	192±93	118±51
Orthostatic Task (n=20)							
HR, beats/min	55.2±8.3	75.4±12.7	76.9±12.3	75.3±11.8	76.0±12.7	77.5±12.6	55.2±8.6
Blood pressure, mm Hg							
Systolic	114.0±7.0	118.8±10.4	119.1±8.6	119.0±8.8	117.9±7.0	118.6±8.3	114.0±9.2
Diastolic	59.3±9.0	69.2±9.8	69.6±7.9	68.2±7.0	69.4±7.2	69.4±7.1	60.6±10.7
NE, nmol/L	1.27±0.76	1.66±0.87	. . .	. . .	. . .	2.50±0.82	1.25±0.60
E, pmol/L	110±45	139±65	. . .	. . .	. . .	190±79	100±44

*HR indicates heart rate; NE, norepinephrine; and E, epinephrine. For heart rate and blood pressure, T1 through T5 refer to measures obtained over five successive 4-minute intervals of each experimental task. For catecholamines, T1 and T5 correspond to concentrations obtained at minutes 3 and 18 of each task.

were conducted on the cholesterol, hemoglobin, and hematocrit values at baseline, during each task period, and on recovery.

As noted above, our third set of analyses sought to determine whether task-evoked changes in cholesterol level, if observed, were independent of hemoconcentration. This was accomplished by correcting cholesterol values arithmetically for plasma volume reduction in instances of hemoconcentration. First, percentage change in plasma volume during each task was calculated from changes in hemoglobin level and hematocrit.[17] (Calculation of changes in plasma volume that use both hemoglobin level and hematocrit may be more accurate than estimates based on hematocrit alone because the latter can be disturbed by hemoconcentration-induced changes in mean red blood cell volume.[18] This method of adjusting lipid values for changes in plasma volume has been used elsewhere.[19]) The corrected task values for cholesterol concentration ($C_{T\text{-}C}$) were then calculated from the measured cholesterol level during the task (C_T) and the estimated percentage change in plasma volume (%dPV) as follows: $C_{T\text{-}C} = C_T/[1-(\%dPV/100)]$.

The corrected serum cholesterol concentrations for each task were then subjected to repeated-measures analysis of variance (again using task order as the between-subject factor and period of measurement as the within-subject factor).

For all repeated-measures analyses of variance, statistical significance is assumed for $P<.05$ (two tailed). Subsequent comparisons among means were performed with the Bonferroni post hoc procedures, at $P<.05$.[20] The repeated-measures analyses yielded no significant effects involving order of task presentation. Therefore, all significant effects described below are based on averaged values collapsed over the two task orders (ie, orthostatic first, mental stress first).

RESULTS

Cardiovascular and Catecholamine Effects of Mental Stress and the Orthostatic Task

The Table contains the cardiovascular and catecholamine measurements obtained during baseline, task, and recovery periods of both the mental stress and orthostatic manipulation. During mental stress, HR, SBP, and DBP increased significantly over baseline values, by averages of 12.3 beats per minute, 9.7 mm Hg, and 5.3 mm Hg, respectively. For the orthostatic task, HR and DBP rose significantly from baseline during standing (mean increase, 21 beats per minute and 10 mm Hg, respectively), while SBP did not rise significantly. During the recovery periods for both tasks, HR, SBP, and DBP returned to baseline values.

In measurement of plasma catecholamines, epinephrine level rose significantly from baseline during minutes 3 and 18 of mental stress (average increase, 72 pmol/L across minutes 3 and 18), whereas norepinephrine level was unaltered by exposure to mental stress. During the orthostatic task, epinephrine concentrations increased significantly at minute 18 (mean increase, 80 pmol/L); norepinephrine level increased significantly from baseline by minute 3 of standing and remained elevated at minute 18, with an average task rise of 0.81 nmol/L. All catecholamine levels returned to baseline during the recovery periods.

Effects of Mental Stress and Orthostatic Task on Cholesterol Level (Uncorrected for Hemoconcentration)

Mean serum cholesterol concentrations during baseline, task, and recovery periods are presented in Fig 1. Cholesterol concentrations during mental stress rose significantly at minute 18 (mean rise from baseline, 0.10 mmol/L [3.7 mg/dL]) and remained significantly elevated during recovery. In contrast, cholesterol concentrations were elevated significantly over baseline values through out the orthostatic task, with an average increase at minute 18 of 0.57 mmol/L (21.9 mg/dL), but did not differ significantly from baseline values during recovery.

Effects of Mental Stress and Orthostatic Task on Hematocrit and Hemoglobin Level

Mean concentrations of hematocrit and hemoglobin obtained during baseline, task, and recovery periods are presented in Fig 2. Hematocrit and hemoglobin level were elevated significantly, relative to baseline measurements, at minutes 3 and 18 of both the mental stress and postural manipulations. As noted above with respect to cholesterol level, hematocrit and hemoglobin level returned to baseline values during the recovery period after standing, but both remained signif-

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icantly elevated over baseline values in the recovery period after mental stress.

Effects of Mental Stress and Orthostatic Task on Cholesterol Level, Corrected for Hemoconcentration

Because both cholesterol concentration and indexes of hemoconcentration rose significantly during task periods, cholesterol values were next corrected for concomitant hemoconcentration by the method described above. Figure 3 depicts the mean concentrations of corrected cholesterol at baseline, task, and recovery periods for both experimental tasks. The absence of any significant alteration during either mental stress or postural change suggests that task-related elevations in *uncorrected* cholesterol concentrations are attributable to hemoconcentration.

COMMENT

While elevated serum cholesterol concentrations confer substantial risk for coronary heart disease, wide intraindividual fluctuation in lipid levels are common,[1,2] and the factors responsible for this variability are poorly understood. Some of this lability may be due to effects of stress on serum lipid concentrations; furthermore, it has been hypothesized that cholesterol level elevation in response to psychological stress is a mechanism through which stress promotes atherosclerosis.[3] However, it is not yet clear whether or how emotional stress raises cholesterol levels.

In this experiment, acute elevations in serum cholesterol concentration were elicited in healthy, young adults, both by exposure to a stressful cognitive task and by assumption of erect body posture. The orthostatic effect replicates previous observations documenting acute increases in the concentration of lipids and many other nondiffusible blood constituents during standing.[10-13] These concentration changes reverse completely with resumption of supine posture. It is thought that increased hydrostatic pressure in the abdomen and legs after movement from supine to standing causes hemoconcentration by forcing fluid out of the intravascular space.[21] As plasma volume is reduced, the concentration of blood cells and other nondiffusible contituents (molecular weight >1000 daltons) passively increases; hemoconcentration (and hemodilution) is completed within 15 to 30 minutes.[10] That cholesterol level elevation during standing is indeed a function of hemoconcentration is further supported in the present investigation by the finding that no alteration in blood cholesterol concentration was evident after arithmetic correction for reduced plasma volume.

Reductions in plasma volume during mental stress were quantitatively small, raising several methodologic issues regarding the measurement of hemoconcentration. Many studies of plasma volume changes rely on either plasma protein concentration or hematocrit alone to index hemoconcentration. Such techniques may underestimate plasma volume shifts because changes in plasma volume are larger than, rather than directly proportional to, hematocrit changes.[22] Additionally, a small but measurable transudation of plasma protein occurs during hemoconcentration, making plasma protein concentrations unreliable.[23,24] Thus, a more accurate index of hemoconcentration may be obtained by using both hemoglobin

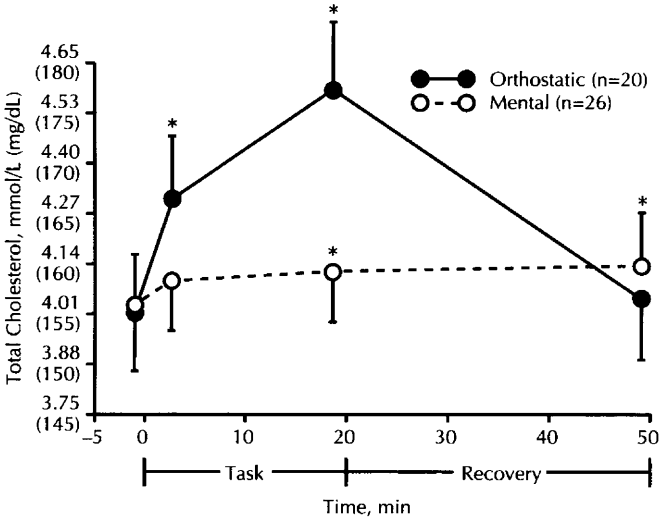
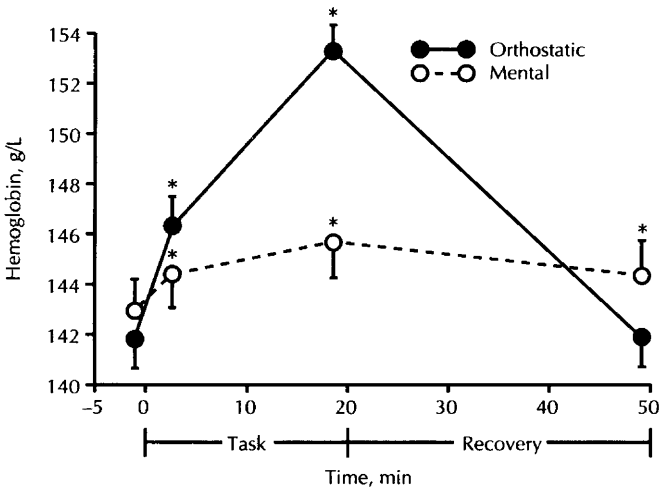


Fig 1.—*Mean concentrations of cholesterol at baseline, during the mental stress and orthostatic manipulations, and at recovery. Subjects were in the reclined position throughout both laboratory sessions except during the task period of the orthostatic challenge. Asterisks indicate P<.05.*



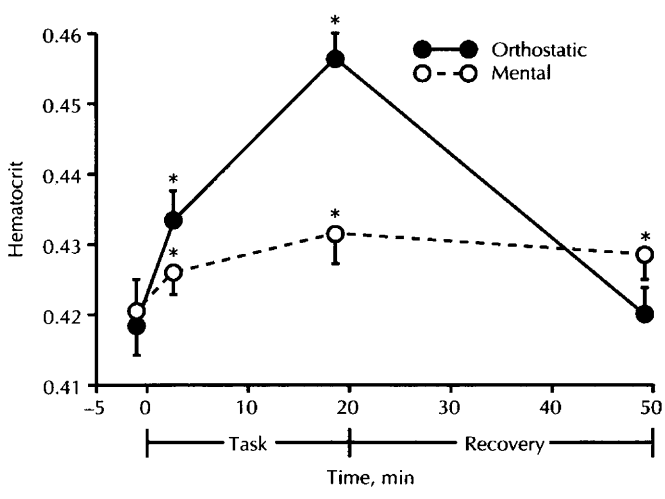


Fig 2.—*Mean concentrations of hemoglobin and hematocrit at baseline, during the mental stress and orthostatic manipulations, and at recovery. Asterisks indicate P<.05.*

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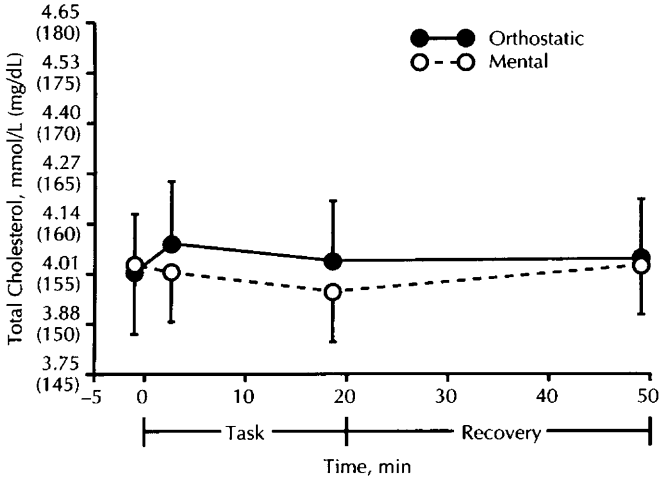

Fig 3.—*Mean concentrations of cholesterol, corrected for concomitant hemoconcentration, at baseline, during mental stress and orthostatic manipulations, and at recovery.*

level and hematocrit. Finally, the commonly employed measurement of hematocrit by the microhematocrit method (which requires visual inspection of the red blood cell mass within a microcapillary tube) is influenced by numerous technical and observer variables and is assumed to be precise only to the nearest whole unit.[25] In contrast, the coefficient of variation of the automatic cell counter employed in this study is typically 0.4% to 0.8%. Automated instruments may therefore be more sensitive to the small changes in hematocrit that accompany brief laboratory manipulations.

This experiment demonstrated that acute mental stress elicits hemoconcentration, as well as significant elevations in serum cholesterol concentration. Our results indicate further that these two effects are related because (as with standing) hemoglobin level and hematocrit closely parallel cholesterol level elevation during acute mental stress, and the increase in cholesterol concentration is attributable to hemoconcentration. The association between naturally occurring life stress and elevated cholesterol levels may also be a function of hemoconcentration, as suggested by the correlation between change in cholesterol concentration and change in hemoglobin concentration among men threatened with unemployment.[8] Therefore, in the cholesterol level elevation after either an administered mental stressor or more protracted life stress, altered lipoprotein metabolism is not necessarily implicated. Nonetheless, the present experiment concerned only acute mental stress, and the effects of acute and chronic stress on both serum lipid levels and atherosclerosis may differ.

The physiologic process leading to reduced plasma volume during mental stress is unknown. It is possible that the increased arterial (hydrostatic) pressure that accompanies mental stress is partially transmitted to the capillaries, leading to a net filtration of fluid out of the intravascular space in a manner comparable with plasma volume reduction with standing. Alternatively, mental stress may reduce blood volume by eliciting a diuresis, as do other manipulations that temporarily increase arterial blood pressure.[26,27] However, data regarding the acute effects of stress on renal function and urine output have been mixed.[28-31] Interestingly, the elevations in hemoglobin level and hematocrit (and cholesterol level) observed during mental stress in the present study failed to reverse in the recovery period. This finding would not be predicted if hemoconcentration during mental stress were attributable solely to fluid filtration driven by temporary blood pressure elevation, but rather is more consistent with the hypothesis that acute stress reduces plasma volume by causing a diuresis.

The results of this investigation have both practical and scientific implications. Blood sampling for lipid levels has become an increasingly casual practice, and this study emphasizes the importance of body posture at the time of sampling. Adherence to the recommended 20-minute rest period in the seated position would largely eliminate this source of cholesterol level variation. This study also indicates that recent stress may be responsible for some portion of day-to-day cholesterol level fluctuation. In terms of atherosclerosis risk, the effects of acute mental stress on serum cholesterol level appear to be both passive (ie, due to hemoconcentration) and quantitatively small. Nonetheless, the cholesterol level elevations elicited by stress were not immediately reversible and could confer increased risk of atherosclerosis. Furthermore, the cholesterol level elevation was accompanied by hemoconcentration, itself potentially pathogenic. An increased hematocrit proportionally increases blood viscosity, which is associated with increased blood pressure and reduced coronary reserve and cerebral blood flow.[32-34] Clinically observed relative polycythemia (Gaisbock syndrome) reflects chronic hemoconcentration and is associated with both hypertension and increased risk for vascular disease.[35] Moreover, in epidemiologic studies, hematocrit correlates with vascular disease risk, independent of traditional risk factors.[36,37]

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