Psychosocial Factors Impair Vascular Responses of Coronary Arteries

J. Koudy Williams, DVM; Joseph A. Vita, MD; Stephen B. Manuck, PhD; Andrew P. Selwyn, MD; and Jay R. Kaplan, PhD

Background. Four sets of monkeys were used to examine the effect of chronic psychosocial disruption and diet on dilator responses of coronary arteries.

Methods and Results. One set consisted of monkeys consuming monkey chow and living in a stable social setting (nonatherosclerotic controls, n=6). Three sets consumed an atherogenic diet for 14 months followed by one of three treatments for the next 16 months: 1) a high-cholesterol diet and housed in unstable social groups (n=9); 2) a low-cholesterol diet and housed in unstable (n=8); or 3) stable groups (n=10). Quantitative coronary angiography revealed that intracoronary infusion of acetylcholine resulted in a change of diameter (versus infusion of 5% dextrose in water) of +4±1% in control monkeys and -11±4% in unstable monkeys consuming a high-cholesterol diet (p<0.05). In monkeys consuming the cholesterol-lowering diet, the change in artery diameter was +2±4% in stable and -10±4% in unstable social conditions (p<0.05) despite a similar plaque size (0.4±0.2 and 0.5±0.1 mm²) and total plasma cholesterol concentrations (179±9 and 172±6 mg/dl), respectively. The arterial response to nitroglycerin was similar among all groups of monkeys.

Conclusions. We conclude that chronic social disruption is associated with relative arterial constriction in response to acetylcholine in atherosclerotic monkeys consuming a cholesterol-lowering diet. (Circulation 1991;84:2146-2153)

Patients with coronary artery atherosclerosis are prone to the development of vasospasm, particularly at sites of coronary artery stenosis.1 Vasospasm, in turn, may contribute to the pathogenesis of myocardial ischemia and infarction.1-4 It has been shown in both humans and monkeys that atherosclerosis may predispose arteries to vasospasm by impairing endothelium-dependent vascular responses of arteries.5-11 Moreover, dietary treatment of atherosclerosis, by lowering plasma cholesterol, reduces plaque size and improves impaired endothelium-dependent vascular responses of atherosclerotic arteries at noncoronary arterial sites.12-14 Endothelium-dependent vasomotor responses, however, may be affected by factors other than the extent of atherosclerosis present. For example, we observed acetylcholine-induced paradoxical constriction of coronary arteries (suggesting endothelial dysfunction) in ovariectomized, atherosclerotic monkeys, while dilation occurred in ovariectomized monkeys matched for atherosclerosis extent but treated chronically with estrogen.15

See p 2201

Results of a study by Yeung et al16 indicate that acute mental stress, produced by an arithmetic challenge, affected vasomotor responses of coronary arteries in coronary artery disease patients with angiographically smooth coronary arteries. In this study, arterial responses to mental stress correlated significantly with responses to acetylcholine. The acute effect of mental stress on vasomotion is not surprising, as mental stress in coronary artery disease patients is known to trigger transient ischemia and regional flow disturbances.17-20 It remains unclear, however, whether chronic stress contributes to the development of vasomotor abnormalities and whether such effects are secondary to or independent of heart rate, blood pressure, plasma lipids, or concomitant plaque size.
The current study was designed as an intervention trial where socially housed atherosclerotic monkeys were exposed to dietary or psychosocial interventions. Quantitative angiography was used to examine endothelium-dependent and-independent dilation of the coronary arteries. Nonatherosclerotic controls were used to determine “normal” responses of coronary arteries to infusion of agonists. The three objectives of this study were to determine 1) whether a high-cholesterol diet plus psychosocial disruption affects endothelium-dependent vascular responses of coronary arteries; 2) whether psychosocial disruption affects endothelium-dependent vascular responses of coronary arteries during dietary lowering of cholesterol; and if so, 3) whether this effect varies with group differences in heart rate, blood pressure, plasma cholesterol, and extent of underlying plaque size.

**Methods**

**Induction and Dietary Treatment of Atherosclerosis**

Thirty-three adult male cynomolgus monkeys (Charles River Research Primates, Port Washington, N.Y.) were used in this study. Six of the monkeys were part of a breeding colony, consumed monkey chow (which is virtually devoid of cholesterol), and lived in stable social groups (membership did not change) for approximately 1 year before the study. These monkeys were used as nonatherosclerotic controls.

The remaining 27 monkeys used in this experiment were part of a larger study involving 100 monkeys. The experimental design of the larger study was a two-step intervention, where atherosclerosis was induced in all monkeys followed by either a dietary or dietary plus psychosocial intervention. Atherosclerosis was induced in all 100 monkeys by means of an atherogenic diet containing 1 mg cholesterol/cal. Plasma cholesterol concentrations were measured every 3 months during the 14-month atherosclerosis induction period. Monkeys were randomized into four groups (25 monkeys per group) with equivalent plasma cholesterol concentrations. The presence and extent of atherosclerosis was confirmed by necropsy and pathological examination of coronary arteries in one group consisting of 25 monkeys at the end of the induction period (baseline necropsy group). Vascular responses were not determined in the baseline necropsy group. Vascular responses were determined in randomly chosen monkeys from the remaining three groups.

**Group 1: High-cholesterol-diet/unstable group (high/cholesterol/unstable).** These monkeys consumed a moderately atherogenic diet (0.20 mg cholesterol/cal and 45% of calories predominantly from saturated fat). They lived in groups of five monkeys each and were subjected to social disruption through monthly reorganization of social group membership. This condition was designed to model a situation in which individuals with preexisting atherosclerosis consume an unhealthy diet and have a behaviorally stressful lifestyle.

**Group 2: Cholesterol-lowering-diet/unstable group (lochol/unstable).** These monkeys consumed a diet based on the American Heart Association (AHA) recommendations (0.05 mg cholesterol/cal and 30% of calories from fat, 10% of the fatty acids from unsaturated fat). They lived in groups of five monkeys each and were subjected to periodic social disruption. This condition was designed to model a situation in which individuals with atherosclerosis undergo plasma cholesterol lowering but maintain a stressful lifestyle.

**Group 3: Cholesterol-lowering-diet/stable group (lochol/stable).** These monkeys consumed the AHA diet, lived in groups of five monkeys each, and were not subjected to periodic social disruption. This condition was designed to model a situation in which individuals with atherosclerosis undergo both plasma cholesterol lowering and a lifestyle modification.

**Plasma Lipids and Lipoproteins**

Venous blood samples were obtained from sedated monkeys (ketamine HCl, 10–15 mg/kg i.m.) at 3-month intervals. The monkeys were sampled in the morning after an overnight fast. Values reported in this study were determined from the blood sample taken at the time of angiography. Total plasma cholesterol (TPC) was measured by the methods of Allain et al.21 and high-density lipoprotein cholesterol (HDL) by the methods described in the Manual of Laboratory Operations of the Lipid Research Clinics Program.22

**Social Stress Manipulation**

We observed previously that coronary artery atherosclerosis in male cynomolgus monkeys is exacerbated when they are exposed to a disrupted social environment.23,24 In those studies, as well as in the current investigation, social disruption or instability was achieved by periodic redistribution of monkeys among social groups that contained five monkeys each. The periodic reorganization of group memberships in the current study was applied to all monkeys in groups 1 and 2, after they had consumed the induction diet and lived in stable social groups for 14 months. The reorganizations every 4 weeks caused each monkey in each cohort to be housed with either three or four new monkeys on every reorganization. Monkeys assigned to group 3 were maintained in stable social groups.

The behavioral repertoire of macaques living in small groups has been described previously by ourselves and others.23–26 To characterize individual behavior in the current study, observations of 30-minute length were made on each monkey in each social group, twice per week. In these observations, data relating to aggressive, submissive, affiliative, and nonsocial interactions were recorded on an electronic data recording device. All observations were made between 9:00 AM and 4:00 PM, with times of day...
balanced across groups. After collection, the data were transmitted to a VAX computer for calculation of either rates of performance (discrete behavioral acts) or percentages of time spent in various activities (behavioral states).

Measurement of Vascular Responses in Coronary Arteries

After 16 months, all monkeys were necropsied for pathological examination of arteries. Immediately before necropsy, 10 randomly chosen monkeys from each treatment group, in addition to the six nonatherosclerotic controls, underwent cardiac catheterization to assess vascular responses of coronary arteries. Usable data were obtained from nine monkeys in group 1 (one monkey died during coronary catheterization); eight monkeys in group 2 (the quality of cineangiograms was poor in two monkeys), 10 monkeys in group 3, and all six control monkeys. Vascular responses were measured on the day of necropsy. Monkeys were anesthetized with ketamine HCl (10–15 mg/kg i.m.) and butorphanol (0.025 μg/kg i.m.). Periodic doses of both agents were given to maintain light anesthesia, and the monkeys were allowed to breathe spontaneously.

A catheter was inserted into the right femoral artery and advanced to the midthoracic aorta for measurement of blood pressure and heart rate. A custom-designed 3F (tapered to 1.8F) catheter (Cook, Inc.) was inserted into the left femoral artery and advanced, under fluoroscopic guidance, into the left main coronary artery as described previously. Blood pressure was monitored from the tip of the coronary catheter to exclude damping and significant obstruction of coronary blood flow.

Using an infusion pump (Harvard, Inc.), serial 2.5-minute intracoronary infusions were made in the following sequence: 1) 5% dextrose in water (control); 2) acetylcholine, 10−8 M, 10−7 M, and 10−6 M (estimated assuming left coronary blood flow of 10 ml/min27); 3) repeat control; and 4) nitroglycerin, 40 μg/min. Hand injections of 2 ml of nonionic contrast ( Omnipaque, Squibb, Princeton, N.J.) were injected for 2 seconds into the left main coronary artery at the end of each drug infusion. There were approximately 10 minutes between interventions. Because of lasting effects of nitroglycerin on blood pressure and heart rate, the order of interventions was not randomized.

Quantitative angiography was performed by an investigator blinded to the monkey’s experimental group. The proximal circumflex (LCX) or left anterior descending (LAD) coronary artery was selected for analysis on the basis of opacification of the vessel and lack of overlapping vessels. The coronary artery segment of interest was digitized at 20–40 μm per pixel using a video camera ( Cohu Inc., San Diego, Calif.), a video interface (Recognition Concepts, Inc.), and a Microvax II computer (Digital Equipment Corp., Maynard, Mass.). Four cine frames were scanned and averaged, two fixed anatomic features serving as references to ensure accurate alignment. Sixteen video images of each cine frame were summed to reduce video noise, and two-line profile averaging was used to minimize anatomic noise. The two fixed anatomic features were also used to ensure accurate registration between different infusions and, therefore, to allow assessment of serial changes in the same arterial segment. From an edge-detection algorithm, a series of measurements of diameter along the length of the arterial segment was derived for each pixel line and the mean diameter of the arterial segment calculated for each infusion.28–30 Diameters were measured twice for each monkey. Values reported are the mean of the measurements, and the two measurements were highly correlated (r=0.8).

Measurement of Coronary Artery Atherosclerosis

Monkeys in groups 1–3 were killed with sodium pentobarbital (80 mg/kg i.v.) following angiography. The cardiovascular system was then flushed with normal saline and perfused with 10% neutral buffered formalin at a pressure of 100 mm Hg for 1 hour. The hearts were immersed in 10% neutral buffered formalin. Although morphometric analysis of plaque size was obtained for three coronary arteries, only data from the LCx or LAD (whichever artery was used for measurements of vascular responses) are reported in this study. Five serial tissue blocks were cut at approximately 3-mm intervals and perpendicular to the long axis of the coronary artery. Histological sections were stained with Verhoeff van Gieson’s stain. These sections were projected, and cross-sectional area of plaque lesion was measured with a digitizer. Atherosclerosis extent was expressed as the mean cross-sectional area of the intima in square millimeters.

Statistical Analyses

Values shown are mean±SEM. To determine whether diet and/or psychosocial factors influenced vascular responses, heart rate, blood pressure, TPC, HDL-C, and plaque size, data were subjected to a series of one-way (Treatment, CONTROL, HICHOL/UNSTABLE, LOCHOL/UNSTABLE, LOCHOL/STABLE) analyses of variance. If data were not distributed normally, they were first subjected to linear transformation.31 Post hoc analyses of data were by Duncan’s multiple comparison procedure. The effect of social disruption on agonistic behaviors among groups was evaluated by means of χ2 analyses.

To determine whether group differences in vascular responses were independent of plaque size, plasma lipids, or cardiovascular parameters, changes in artery diameter in response to acetylcholine were corrected for intimal area (plaque extent), TPC, HDL, resting heart rate, and blood pressure by analysis of covariance. Percent change in artery diameter was the dependent variable, and intimal area, TPC, HDL, heart rate, or blood pressure were the covariates.
Table 1. Effect of Diet and Social Disruption on Plasma Lipids and Plaque Size

<table>
<thead>
<tr>
<th></th>
<th>TPC (mg/dl)</th>
<th>HDLC (mg/dl)</th>
<th>TPC/HDLC</th>
<th>IA (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>95±10</td>
<td>51±6</td>
<td>2±0.03</td>
<td>...</td>
</tr>
<tr>
<td>Lochol/</td>
<td>327±33*</td>
<td>35±4*</td>
<td>11±2*</td>
<td>1.2±0.07</td>
</tr>
<tr>
<td>unstable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lochol/</td>
<td>172±6†</td>
<td>57±5†</td>
<td>3±0.4†</td>
<td>0.5±0.2†</td>
</tr>
<tr>
<td>stable</td>
<td>179±9†</td>
<td>65±4†</td>
<td>3±0.2†</td>
<td>0.4±0.1†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. TPC, total plasma cholesterol; HDLC, high density lipoprotein cholesterol; IA, plaque size of left circumflex coronary artery.
*p<0.05 vs. Control; †p<0.05 vs. Lochol/unstable.

Results

Plasma Lipids

TPC and HDLC concentrations during the atherosclerosis induction phase of the experiment were approximately 650 mg/dl and 22 mg/dl, respectively. Responses of plasma lipids to treatment are found in Table 1. A series of one-way (TreatmentCONTROL, HICHOIJUNSTABLE, LOCHOLUNSTABLE, LOCHOSTABLE) analysis of variance revealed a significant treatment effect on TPC (F3,29=5.48, p=0.021), HDLC (F3,29=4.89, p=0.025), and TPC/HDLC (F3,29=5.74, p=0.013) (Table 1). Monkeys eating monkey chow or the cholesterol-lowering diet had lower TPC and higher HDLC concentrations and a less atherogenic TPC/HDLC ratio than unstable monkeys eating the high-cholesterol diet (p<0.05) (Table 1). As expected, consuming the cholesterol-lowering diet lowered TPC, increased HDLC concentrations, and decreased TPC/HDLC compared with unstable monkeys consuming the high-cholesterol diet, regardless of social condition (stable or unstable). Social condition did not alter the plasma lipid profile of monkeys consuming the cholesterol-lowering diet (p>0.05) (Table 1).

Atherosclerosis Extent

Nonatherosclerotic monkeys were not necropsied, hence lesion extent was not measured in these monkeys. However, it has been shown previously that the coronary arteries of similarly treated monkeys are thin-walled and without gross or microscopic evidence of atherosclerosis (intimal area<0.01 mm²).13

In monkeys consuming the high-cholesterol diet, epicardial coronary arteries were thickened compared with those of monkeys fed chow. Thickening of arteries was due primarily to an increase in cross-sectional area of the intima (Table 1). In monkeys consuming the cholesterol-lowering diet, there was a loss of lipid from the intimal lesions, but the fibrous component of the intima was increased.

The effect of treatment on plaque size is depicted in Table 1. One-way (TreatmentCONTROL, HICHOIJUNSTABLE, LOCHOLUNSTABLE, LOCHOSTABLE) analysis of variance revealed a significant treatment effect on plaque size (F2,24=4.24, p=0.03). As expected, the intimal area of coronary arteries from monkeys consuming the cholesterol-lowering diet was smaller than among monkeys eating the high-cholesterol diet, regardless of social conditions (p<0.05) (Table 1). The intimal area of the coronary arteries of the monkeys consuming the cholesterol-lowering diet was similar, at least in this subset of individuals, regardless of social condition (stable or unstable) (p>0.05).

Cardiovascular Parameters

Table 2 lists blood pressures and heart rates of the four groups of monkeys during infusion of 5% dextrose and during infusion of acetylcholine and nitro-glycerin. Only responses to infusion of 10⁻⁶ M acetylcholine are presented because infusion of 10⁻⁸ M or 10⁻⁷ M acetylcholine did not change diameter of coronary arteries in any group of monkeys. A series of one-way (TreatmentCONTROL, HICHOIJUNSTABLE, LOCHOLUNSTABLE, LOCHOSTABLE) analyses of variance applied to the infusion data revealed no significant baseline differences among treatment groups in blood pressure (F3,29=1.85, NS) or heart rate (F3,29=1.26, NS). However, monkeys housed in unstable social conditions tended to have higher blood pressures and heart rates than monkeys housed in stable social conditions (Table 2). There were no significant effects of treatment on blood pressure or heart rate associated with infusion of any of the agonists or with infusion of 5% dextrose (control) (F<2.0, p>0.2 for all). However, post hoc analysis (Duncan's multiple

Table 2. Effect of Diet and Social Disruption on Heart Rate and Blood Pressure

<table>
<thead>
<tr>
<th></th>
<th>C1 HR</th>
<th>C1 BP</th>
<th>ACH HR</th>
<th>ACH BP</th>
<th>C2 HR</th>
<th>C2 BP</th>
<th>TNG HR</th>
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<td>Control</td>
<td>145±10</td>
<td>70±5</td>
<td>125±17*</td>
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<td>147±11</td>
<td>75±6</td>
<td>152±10</td>
<td>62±6*</td>
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<td>Hichol/</td>
<td>165±15</td>
<td>85±5</td>
<td>137±10*</td>
<td>80±8*</td>
<td>157±8</td>
<td>89±6</td>
<td>157±10</td>
<td>83±6*</td>
</tr>
<tr>
<td>unstable</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lochol/</td>
<td>167±10</td>
<td>87±7</td>
<td>147±11*</td>
<td>77±7*</td>
<td>162±13</td>
<td>91±4</td>
<td>167±14</td>
<td>80±6*</td>
</tr>
<tr>
<td>unstable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lochol/</td>
<td>150±8</td>
<td>75±8</td>
<td>108±20*</td>
<td>63±3*</td>
<td>145±12</td>
<td>75±4</td>
<td>147±11</td>
<td>67±5*</td>
</tr>
<tr>
<td>stable</td>
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</table>

Values are mean±SEM. C1, infusion of 5% dextrose in water; ACH, acetylcholine; C2, recontrol; TNG, nitroglycerin; HR, heart rate (beats/min); BP, blood pressure (mm Hg).
*p<0.05 vs. control.
comparison procedure) indicates that blood pressure decreased significantly during infusion of both acetylcholine and nitroglycerin in all groups of monkeys compared with that measured during infusion of 5% dextrose (p<0.05) (Table 2). Heart rate decreased significantly in all groups of monkeys during infusion of acetylcholine compared with that measured during infusion of 5% dextrose (p<0.05) (Table 2).

Endothelium-Dependent and -Independent Vascular Responses

Figure 1 depicts vascular responses to 10⁻⁶ M acetylcholine. A series of one-way (Treatment: CONTROL, HICHOL/UNSTABLE, LOCHOL/UNSTABLE, LOCHOL/STABLE) analyses of variance applied to the infusion data revealed a significant treatment effect on vascular response to acetylcholine (F3,29=4.70, p=0.01).

The change in diameter of coronary arteries produced by infusion of 10⁻⁶ M acetylcholine in the four groups of monkeys (control, hichol/unstable, lochol/unstable, and lochol/stable) were +4±1%, -11±4%, -10±4%, and +2±4% respectively, where “+” indicates relative dilation and “−” indicates relative constriction compared with arterial diameter measured during infusion of 5% dextrose in water. Post hoc comparisons revealed that vascular responses to acetylcholine were significantly different between control and hichol/unstable groups (p<0.05). Vascular responses to acetylcholine were similar between control and lochol/stable groups (p>0.05) or between hichol/unstable and lochol/unstable groups (p>0.05). However, psychosocial disruption resulted in significantly different vascular responses between the two groups of monkeys consuming the cholesterol-lowering diet (p<0.05). There were no significant treatment effects on vascular responses associated with infusion of nitroglycerin (F<2.0 for all, NS) (Figure 2).

Analysis of covariance indicates that, after adjustment for TPC, HDLC, and plaque size (intimal area), differences in vascular responses to acetylcholine still exist among groups (F1,16=4.75, p=0.02; F1,16=5.33, p=0.02; and F1,16=4.27, p=0.03, respectively). Furthermore, analysis of covariance indicates that, after adjustment for group differences in baseline blood pressure and heart rate, differences in vascular response to acetylcholine still exist among groups (F1,16=3.95, p=0.04; F1,16=4.37, p=0.04, respectively). Finally, results indicate that individual differences in vascular responses to acetylcholine are not highly associated with individual differences in plaque size (r=0.30), blood pressure (r=0.02), heart rate (r=0.20), or plasma cholesterol (r=0.15).

Behavioral Responses to Repeated Social Disruption

Social reorganization resulted in significant differences in the aggressive behavior of the monkeys. Specifically, analysis of 3,385 fights over 26 months indicated that, upon reorganization, the unstable monkeys of both dietary conditions engaged in a greater percentage as well as number of fights involving physical contact than did their counterparts living in the stable social groups (percentage of fights involving contact: 10.3% unstable versus 6.0% stable, χ²=18.2, p<0.01; number of fights involving contact: 167 unstable versus 110 stable, χ²=12.0, p<0.01). Neither of these behavioral indexes was correlated with extent of vascular response. Unstable monkeys in both dietary cohorts also engaged in more passive body contact than did monkeys in stable groups during the 26 months before the vascular evaluations (χ²=11.42, p<0.01). This behavior was significantly associated with extent of vascular response to acetylcholine (ρ=−0.39, p=0.05), indicating that as monkeys engaged in increased passive body contact (sitting in physical contact without any social behavior), their arteries tended toward relative constriction.
Discussion

The four major findings of this study were that among monkeys initially subjected to a highly atherogenic diet, 1) the combination of a high-cholesterol diet and an unstable social condition resulted in larger plaques and relative constriction of coronary arteries in response to acetylcholine compared with nonatherosclerotic controls; 2) the combination of a low-cholesterol diet and an unstable social condition resulted in relatively small plaques but vascular responses similar to those of unstable monkeys consuming a high-cholesterol diet; 3) the combination of a low-cholesterol diet and a stable social condition also resulted in relatively small plaques but vascular responses similar to those of nonatherosclerotic controls; and 4) the vascular responses to acetylcholine of unstable and stable monkeys consuming a low-cholesterol diet were significantly different despite similar TPC concentrations, HDLC concentrations, plaque sizes, baseline heart rates, and blood pressures. Results of this study are the first to show that chronic “stressors” may impair endothelium-dependent vascular responses of coronary arteries.

The observation that intracoronary infusion of acetylcholine causes constriction of coronary arteries of socially disrupted monkeys consuming a high-cholesterol diet is consistent with those of several studies that show that atherosclerosis impairs endothelium-dependent vascular responses of coronary arteries of humans8 and in the hind limb and cerebral circulation of cynomolgus monkeys.9-11 It cannot be determined from this study whether psychosocial factors exacerbated endothelial dysfunction in atherosclerotic coronary arteries of monkeys consuming the high-cholesterol diet.

We report here that modest lowering of plasma cholesterol of atherosclerotic monkeys housed in stable social conditions resulted in endothelium-dependent vascular responses of coronary arteries similar to those of nonatherosclerotic controls. This finding is consistent with those of previous studies that show that consumption of monkey chow results in a marked reduction of plasma cholesterol concentrations in monkeys with established atherosclerosis and improves endothelium-dependent vascular responses at several noncoronary artery sites.12-14 In the current experiment, however, monkeys consuming a cholesterol-lowering diet, but exposed to an unstable social environment, had endothelium-dependent acetylcholine responses similar to those of unstable monkeys consuming a high-cholesterol diet. The difference in vascular response of stable and unstable monkeys consuming a cholesterol-lowering diet indicates that social disruption prevented the “return” of vascular responses toward those of nonatherosclerotic controls.

Since the difference in vascular response to acetylcholine between groups of monkeys consuming a cholesterol-lowering diet was independent of group differences in blood pressure, heart rate, plasma lipids, and plaque extent, these data suggest that the “stress” of chronic social disruption impairs endothelium-dependent dilation of coronary arteries during dietary lowering of plasma cholesterol. However, the specific pathophysiologic mechanisms linking “stress” and endothelial dysfunction remain to be identified.

Effects of Psychosocial Factors on the Pathogenesis of Coronary Heart Disease

Results of previous studies from our laboratory indicate that chronic stress elevates heart rate and exacerbates coronary artery atherosclerosis in monkeys.32 Blockade of β-adrenergic receptors with propranolol inhibits the atherogenic effects of chronic stress,33 suggesting that chronic sympathetic arousal may contribute to the pathogenesis of atherosclerosis during chronic stress. In the present experiment, blood pressure and heart rate tended to be higher in monkeys housed in unstable social groups. However, the effect of stress on these cardiovascular parameters was small and did not explain group differences in vascular responses.

The behavioral data from the present experiment indicate that the reorganization manipulation was accompanied by significant increases in measures of aggressiveness (contact aggression) and affiliation (passive body contact). The latter behavior was also correlated significantly (in a negative direction) with vascular responses to acetylcholine. It is not clear from the correlation analysis, however, whether this behavior, associated behaviors, or the physiological concomitants of such behaviors contributed to the pattern of observed vascular responses.

Numerous mechanisms may have mediated the effect of chronic stress on vasomotor responses of coronary arteries. In a preliminary study, Rebecca et al34 reported direct angiographic evidence of coronary vasoconstriction at the site of atherosclerosis during the performance of a mental arithmetic task. Results of the study by Petterson et al35 indicate that acute stress, produced by chloralose anesthesia, injures the vascular endothelium of rabbits. In 1980, Furchgott and Zawadzki36 determined that intact, functional vascular endothelium is necessary for normal dilation of arteries. Recently, Yeung et al16 compared the response of coronary arteries with acute episodes of stress and acetylcholine infusion in patients undergoing angiography for suspected coronary artery disease. They found that coronary vasomotion during mental stress correlated with the endothelium-dependent response of coronary arteries to acetylcholine. Results of these studies suggest that impaired endothelium-dependent vascular responses of coronary arteries may contribute to episodes of myocardial ischemia during acute periods of stress.

Results of a previous experiment in our laboratory indicate that social disruption of monkeys results in a modest increase in heart rate and damage to the vascular endothelium, which is reduced by blockade
of β-adrenergic receptors.33 We speculate that monkeys housed in unstable social groups may have repeated acute episodes of sympathetic stimulation during confrontations with other animals. Significant increases in catecholamine secretions, blood pressure, and heart rate occur during laboratory-induced mental stress.37–39 Repeated episodes of acute sympathetic stimulation probably result in sharp increases in blood pressure and heart rate, which may damage vascular endothelium and impair endothelium-dependent vasomotion.

**Limitations of the Study**

The design of this experiment did not include a group of monkeys fed a high-cholesterol diet and housed in stable social conditions. Inclusion of this group would have permitted evaluation of a regression diet on vascular responses. However, it is reasonable to speculate that consumption of a regression diet would improve endothelium-dependent dilation in coronary arteries, since it has been shown in previous studies that atherosclerosis impairs9–11 and regression of atherosclerosis improves12–14 vascular responses at other noncoronary artery sites.

It was not possible, for logistic reasons, to do repeat measures of vascular responses throughout the experiment. However, presentation of results in a between-subjects design does not affect the conclusions of this study. Infusions of agonists were given in the same order in each monkey. Therefore, a time-associated or carryover effect cannot be ruled out. However, even if there were a substantial carryover effect, this would not negate the conclusions of the study regarding the differences in the four experimental groups. Only acetylcholine was used as the endothelium-dependent agonist. Therefore, it cannot be determined from this study whether stress impaired endothelium-dependent dilation in general or whether the effect of stress is specific to acetylation (i.e., muscarinic receptors).

**Conclusions**

A direct link between emotional-stress–induced endothelial dysfunction and clinical myocardial ischemia remains to be established. However, results of the present study suggest that chronic social disruption potentiates the functional alterations that may underlie the clinical expression of coronary heart disease. Such data may be of considerable importance in helping to resolve current uncertainty regarding the role of psychosocial factors (such as the type “A” behavior pattern or hostility) in the etiology of coronary heart disease in humans.

**References**


Key Words • atherosclerosis • vasospasm • stress
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