Social Status and Coronary Artery Atherosclerosis in Female Monkeys

Carol A. Shively, Thomas B. Clarkson

Abstract While coronary heart disease is the leading cause of death in women in the United States, research in the area is lacking, especially concerning psychosocial risk factors. The purpose of this experiment was to study the effect of a known psychosocial risk factor in female monkeys, social status, and the effect of alteration of social status on coronary artery atherosclerosis. In previous experiments it has been demonstrated that social status is an enduring characteristic of the individual and that socially subordinate female monkeys have poor ovarian function and exacerbated coronary artery atherosclerosis. In the present experiment, adult female monkeys were fed an atherogenic diet and housed in small social groups, and social status was altered in half of the animals (subordinates became dominant and dominants became subordinate). The manipulation of social status had minimal effects on risk factors but significantly affected coronary artery atherosclerosis, supporting the hypothesis that social status affects atherogenesis in these females. However, all animals that changed social positions had worsened coronary artery atherosclerosis whether they became dominant or became subordinate, and this effect was independent of ovarian function. Subordinates that became dominant had 44% more and dominants that became subordinate had 500% more atherosclerosis than their counterparts that did not change social status. Thus, modification of this psychosocial risk factor was not effective in reducing coronary artery atherosclerosis. The manipulation of social status may have deleteriously altered a complex interaction between individuals and their psychosocial environment.

Key Words • females • psychosocial risk factor modification • animal model • coronary artery atherosclerosis • Macaca fascicularis • ovarian function

Psychosocial factors may increase the risk of coronary heart disease in women. Female cynomolgus monkeys (Macaca fascicularis) have been used for several years to identify psychosocial factors associated with coronary heart disease and to understand the mechanisms through which these factors increase coronary heart disease risk. This species is a useful animal model because, like humans, females are protected against coronary artery atherosclerosis (CAA) relative to their male counterparts, they have menstrual cycles similar in length and hormonal fluctuations to those of women, and they rely on complex social relationships. Previously, it was reported that adult female cynomolgus monkeys that are socially subordinate have more extensive CAA than socially dominant females. Additionally, subordinate females have impaired ovarian function, characterized by fewer menstrual cycles and lower sex steroid concentrations than dominant females. Thus, it was hypothesized that social subordination may impair ovarian function and increase atherogenesis. It was not clear from previous studies whether there was an effect of social status on CAA independent of ovarian function.

Social status is important to the individual because it has physiological as well as behavioral ramifications. Socially subordinate females are thought to be stressed because their adrenal glands hypersecrete cortisol, they are frequent subjects of aggression, and they spend considerable time alone, ie, socially isolated. Intriguingly, social status appears to be a reliable characteristic of the individual. It has been observed that among females that live for a short period in each of a series of social groups, those that were dominant in the first social group were typically dominant in subsequent social groups. Likewise, those that were subordinate in the first social group typically were subordinate in subsequent social groups.

In the experiment reported here, it was hypothesized that if social subordination causes exacerbation of atherosclerosis, then altering social status should result in a change in extent of atherosclerosis. If dominants became subordinate increased atherosclerosis would be expected, whereas if subordinates became dominant decreased atherosclerosis would be expected. Thus, we chose to manipulate social status, a known psychosocial risk factor, and measure the effect on CAA in adult females housed in social groups. Manipulation of social status may be expected to alter behavioral responses as well as involve a change in the social environment. In addition to examining the effects of psychosocial risk factor modification, this experiment provides further evidence addressing the nature of the relationship between social status and CAA in females.

Methods

Subjects

Forty-eight adult female monkeys were obtained from Charles River Research Primates. The animals were estimated to be 6 to 12 years of age based on dentition. These females were chosen from a pool of 72 adult female monkeys that were fed the experimental diet (described below) for 1 month before the onset of the experiment. Total plasma cholesterol (TPC) and high-density lipoprotein (HDL) cholesterol concentrations were determined using the methods described below, and monkeys falling in the upper two thirds of the distribution of the ratio of TPC to HDL (TPC-HDL) choles-

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terol were chosen for study. These females were selected to represent the subset of the adult female population that is at increased risk of developing atherosclerosis. Six animals died from causes unrelated to the experiment (primarily diarrheal diseases), resulting in 42 study animals.

**Diet**

The monkeys were fed a moderately atherogenic diet that contained 0.25 mg cholesterol per calorie and 40% of calories as fat (Table 1) ad libitum for 32 months. Based on previous studies this diet was expected to induce moderate hypercholesterolemia and significant amounts of atherosclerosis in the coronary arteries.10

**Experimental Design**

The experimental design is depicted in Fig. 1. The monkeys began consuming the atherogenic diet 1 month before the onset of the experiment to aid subject selection (see above) and continued to consume this diet throughout the experiment. They were housed for 3 months in single cages when preexperimental measures of plasma cholesterol concentrations, adiposity, carbohydrate metabolism, and blood pressure were collected (preexperimental phase). The details of the sampling procedures are described below. The monkeys were then assigned randomly to four-member social groups for 8 weeks (experimental phase 1) during which social status stabilized and was determined (initial social status). First- and second-ranking females were considered dominant, and third- and fourth-ranking females were considered subordinate. Animals were then assigned to new social groupings of four animals each, based on their social status, for 26 months (experimental phase 2). Animals that were previously dominant (two first- and two second-ranking monkeys) were housed together, and animals that were previously subordinate (two third- and two fourth-ranking monkeys) were housed together. Linear social status hierarchies reformed: half of the subordinate animals became dominant, and half of the dominant animals became subordinate (manipulated social status). This manipulation resulted in a change in social status in half of the animals: those that were initially subordinate and became dominant and those that were initially dominant and became subordinate.

**Sampling Procedures**

Several known or suspected atherosclerosis risk variables were measured periodically throughout the preexperimental phase and experimental phase 2. All procedures involving animals were performed in accordance with federal and state regulations and with the approval of the institutional animal care and use committee.

**Plasma Cholesterol Concentrations**

TPC and HDL cholesterol concentrations were determined once during the preexperimental phase and every 4 months during experimental phase 2.11 Multiple measures made during experimental phase 2 were averaged for analysis.

**Adiposity**

Anthropometric measures of adiposity were taken once during the preexperimental phase and every 4 months during experimental phase 2. Body weight (BW) and body mass index (BMI, measured as BW/ventral trunk length in square centimeters) were measured. Subscapular, suprailliac, triceps, and thigh skinfolds were measured using spring-loaded calipers, and waist, hip, and thigh circumferences were measured using a steel tape measure.12 Multiple measures made during experimental phase 2 were averaged for analysis.

**Carbohydrate Metabolism**

Blood glucose and insulin concentrations were determined, following an 18-hour fast, during the preexperimental phase and during experimental phase 2.14,15

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**Table 1. Diet Composition**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount, g/100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casein, USP</td>
<td>8.0</td>
</tr>
<tr>
<td>Lactalbumin</td>
<td>8.0</td>
</tr>
<tr>
<td>Wheat flour</td>
<td>35.4</td>
</tr>
<tr>
<td>Dextrin</td>
<td>6.0</td>
</tr>
<tr>
<td>Sucrose</td>
<td>5.0</td>
</tr>
<tr>
<td>Applesauce</td>
<td>4.5</td>
</tr>
<tr>
<td>Lard</td>
<td>9.5</td>
</tr>
<tr>
<td>Butter</td>
<td>3.0</td>
</tr>
<tr>
<td>Beef tallow</td>
<td>7.0</td>
</tr>
<tr>
<td>Dry egg yolk</td>
<td>3.5</td>
</tr>
<tr>
<td>Safflower oil</td>
<td>0.5</td>
</tr>
<tr>
<td>Complete vitamin mixture</td>
<td>2.6</td>
</tr>
<tr>
<td>Ausman-Hayes mineral mixture</td>
<td>5.0</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Adapted from Reference 10.
Blood Pressure

Systolic (SBP) and diastolic (DBP) blood pressures were measured once during the preexperimental phase and every 4 months during experimental phase 2. Multiple measures made during experimental phase 2 were averaged for analysis.

Menstrual Cycle Determinations

The monkeys were trained to present themselves for vaginal swabbing to detect menses and for femoral venipuncture for blood sample collection three times a week throughout experimental phase 2. Blood samples were used for progesterone determination by radioimmunoassay (Diagnostic Products Corp). Luteal-phase progesterone concentration was used as an indicator of the quality of a menstrual cycle. High progesterone concentrations (>4 ng/mL) indicate that ovulation has occurred, whereas low progesterone concentrations (<2 ng/mL) indicate an anovulatory cycle.17,18 The highest progesterone value found during the luteal phase was used to represent that menstrual cycle, and mean peak progesterone concentrations were calculated for analysis. Average cycle length and the number of cycles each female had during experimental phase 2 were also calculated for analysis.

Social Status

The social status of an individual refers to that individual’s ability to defeat other members of its social group in agonistic or competitive interactions. Social status was determined monthly throughout experimental phases 1 and 2 by recording the outcomes of aggressive interactions between cage mates. The animal in each social group that defeated all other group members was designated the first-ranking monkey. The animal that defeated all but the first-ranking monkey was designated the second-ranking monkey, and so forth. The resulting social status hierarchies for each social group were stable over time.9

Monkeys that changed social status when their social environment was altered also changed their behavior. Those that were subordinate and became dominant defeated the majority of individuals in their final social group, whereas those that were dominant and became subordinate were defeated by the majority of others in their final social group.

Necropsy and Measurement of Atherosclerosis

At the time of necropsy, the animals were anesthetized deeply with pentobarbital (60 mg/kg). Each cardiovascular system was flushed with normal saline and perfused with 10% neutral buffered formalin under a pressure of 100 mm Hg. After pressure fixation, five serial blocks were taken from each of the left circumflex, left anterior descending, and right coronary arteries. One section from each block was stained with Verhoeff-van Gieson’s stain and projected, and the area occupied by the intima and intimal lesion was measured in square millimeters with a digitizer by a technician blinded to the experimental group assignments of the animals.19 The mean of the 15 sections from the three arteries was calculated for analysis.

Statistical Analysis

Logarithmic transformation of all variables was used to reduce skewness and equalize group variances. Unless otherwise indicated, all data presented are untransformed values in the original units derived from the mean of the transformed distribution. Pearson’s r correlation, 2x2 (initial status x manipulated status) ANOVA and ANCOVA, and multiple regression were used for statistical analyses. All probability values are the result of two-sided tests. A value of P<.05 was considered significant.

Table 2. Preexperimental Mean Values of Coronary Artery Atherosclerosis Risk Factors

<table>
<thead>
<tr>
<th>Manipulated Social Status</th>
<th>Initial Social Status</th>
<th>Subordinate</th>
<th>Dominant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub (n=12)</td>
<td>Dom (n=8)</td>
<td>Sub (n=11)</td>
<td>Dom (n=11)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>3.0</td>
<td>3.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>40.4</td>
<td>40.1</td>
<td>40.7</td>
</tr>
<tr>
<td>Thigh circumference, cm</td>
<td>12.8</td>
<td>12.3</td>
<td>12.0</td>
</tr>
<tr>
<td>Total plasma cholesterol, mg/dL</td>
<td>344</td>
<td>312</td>
<td>325</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>42.5</td>
<td>36.4</td>
<td>41.0</td>
</tr>
<tr>
<td>TPC-HDL cholesterol ratio*</td>
<td>8.1</td>
<td>8.6</td>
<td>7.9</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>65.4</td>
<td>69.1</td>
<td>61.2</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>28.8</td>
<td>48.3</td>
<td>27.3</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>91</td>
<td>106</td>
<td>88</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>56</td>
<td>69</td>
<td>55</td>
</tr>
</tbody>
</table>

Sub indicates subordinate; Dom, dominant; HDL, high-density lipoprotein; and TPC, total plasma cholesterol.

*Significant preexperimental predictors of coronary artery atherosclerosis extent (P<.05).

Results

Preexperimental Phase Characteristics of the Animals

Preexperimental measures of risk factors suggested that there was little difference between experimental groups before the onset of the experiment (Table 2). Plasma lipid and glucose concentrations did not differ between experimental groups during the preexperimental phase. SBP appeared to be slightly higher in females that were initially subordinate (effect of initial social status, P<.07), and insulin concentrations tended to be higher during the preexperimental phase in those females that became dominant in the experimental phase (effect of manipulated social status, P<.08); however, neither of these reached significance. Most measures of adiposity also were not different. However, among initially subordinate animals, those that became dominant had smaller thigh circumferences, whereas among initially dominant animals, those that became subordinate had larger thigh circumferences (initial social status x manipulated social status interaction, P<.02).

Preexperimental values of plasma cholesterol concentrations were significantly associated with CAA extent (TPC, r=.34; HDL cholesterol ratio, r=-.30; TPC-HDL cholesterol: r=.38; all P<.05). No other risk variables measured during the preexperimental phase were associated with CAA.

Changing Social Status and CAA Extent

The extent of CAA found in each female in each group is depicted in Fig 2. After transformation to reduce the skewness and heterogeneity of variance, ANOVA revealed a significant interaction effect (initial
social status × manipulated social status interaction, \( P < .03 \)). Among initially subordinate females, those that became dominant had somewhat more extensive CAA, whereas among initially dominant females, those that became subordinate had more extensive CAA.

Although the experimental groups had quite similar risk factor values before the onset of the experiment, small differences between the groups were present, particularly in thigh circumference. To control for small differences present before the onset of the experiment and to reduce variability, the means of all potential risk factors that were measured during the preexperimental phase were entered as eligible predictors in a multiple regression analysis (after grouping variables of \( P < .10 \)) of CAA extent (Table 2). The preexperimental ratio of TPC-HDL cholesterol (\( P = .01 \)) and thigh circumference (\( P = .05 \)) were significant preexperimental predictors of CAA extent and together accounted for 35% of the variance in CAA.

To control for this variation in preexperimental risk factors and to reduce variability caused by individual differences within experimental groups, we used ANCOVA to examine the effects of initial and manipulated social status, adjusted for significant preexperimental risk factors (thigh circumference and ratio of TPC-HDL cholesterol). These adjusted mean values of CAA extent represent the best estimate of the overall effect of social status and changing social status on CAA (Fig 3). Among initially subordinate females, those that became dominant had 44% greater CAA extent than subordinates that did not change social status. However, among initially dominant females, those that became subordinate had 500% greater CAA extent than those that did not change social status (initial social status × manipulated social status interaction, \( P < .006 \)). Thus, females that changed social status had worsened atherosclerosis irrespective of whether they were dominant or subordinate for the 26 months they lived in their final social groups. Those that were initially dominant and became subordinate were most deleteriously affected.

**Risk Factors and CAA in Experimental Phase 2**

There were relatively few differences between the experimental groups in risk factors measured during experimental phase 2 (Table 3). Glucose concentrations were slightly lower in females that were initially subordinate (effect of initial social status glucose, \( P < .04 \)). Among initially subordinate animals, those that changed social status had worsened atherosclerosis irrespective of whether they were dominant or subordinate for the 26 months they lived in their final social groups. Those that were initially dominant and became subordinate were most deleteriously affected.

**TABLE 3. EXPERIMENTAL PHASE 2 VALUES OF CORONARY ARTERY ATHEROSCLEROSIS RISK FACTORS**

<table>
<thead>
<tr>
<th>Initial Social Status</th>
<th>Manipulated Social Status</th>
<th>Sub (n=12)</th>
<th>Dom (n=8)</th>
<th>Sub (n=11)</th>
<th>Dom (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td></td>
<td>3.1</td>
<td>3.2</td>
<td>3.0</td>
<td>3.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td>41.1</td>
<td>43.4</td>
<td>42.0</td>
<td>42.0</td>
</tr>
<tr>
<td>Thigh circumference, cm</td>
<td></td>
<td>13.5</td>
<td>13.1</td>
<td>13.3</td>
<td>13.8</td>
</tr>
<tr>
<td>Total plasma cholesterol, mg/dL</td>
<td></td>
<td>345</td>
<td>303</td>
<td>363</td>
<td>323</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td></td>
<td>49.4</td>
<td>46.3</td>
<td>46.5</td>
<td>54.4</td>
</tr>
<tr>
<td>TPC-HDL cholesterol ratio*</td>
<td></td>
<td>7.9</td>
<td>8.0</td>
<td>9.1</td>
<td>7.0</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td></td>
<td>55.2</td>
<td>56.3</td>
<td>59.2</td>
<td>64.4</td>
</tr>
<tr>
<td>Insulin*, μU/mL</td>
<td></td>
<td>16.5</td>
<td>20.9</td>
<td>30.1</td>
<td>20.8</td>
</tr>
<tr>
<td>Systolic blood pressure†, mm Hg</td>
<td></td>
<td>104</td>
<td>114</td>
<td>105</td>
<td>98</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td></td>
<td>63</td>
<td>71</td>
<td>62</td>
<td>56</td>
</tr>
<tr>
<td>Progesterone§, ng/mL</td>
<td></td>
<td>5.8</td>
<td>9.7</td>
<td>7.6</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Sub indicates subordinate; Dom, dominant; HDL, high-density lipoprotein; and TPC, total plasma cholesterol.
*Significant experimental phase 2 correlates of coronary artery atherosclerosis extent (\( P < .01 \)).
†Initial social status × manipulated social status interaction (\( P < .05 \)).
‡Initial social status (\( P < .05 \)).
§Manipulated social status (\( P = .02 \)).
status and became dominant had higher blood pressures. Among initially dominant animals, those that changed social status and became subordinate had higher blood pressures (initial social status×manipulated social status interaction: for SBP, P<.03; for DBP, P=.05). There were no differences in adiposity or in any measures of plasma cholesterol (TPC, HDL, or TPC-HDL cholesterol ratio) or insulin concentrations (2×2 ANOVA, all P>.10). However, mean peak luteal-phase progesterone concentrations were higher in females that were dominant in their manipulated social groupings, indicating an overall higher quality of ovarian function relative to their subordinate counterparts (manipulated social status, P=.02).

Plasma cholesterol and insulin concentrations in experimental phase 2 were significantly associated with CAA extent (TPC, r=.59; HDL cholesterol, r=−.43; TPC-HDL cholesterol ratio, r=.65; insulin, r=.39; all P<.01). No other risk variables measured during experimental phase 2 were associated with CAA extent (all P>.10).

To determine whether any of the risk factors measured during the experimental phase could have accounted for the effects of social status on CAA, all experimental phase 2 risk factors that, in addition to preexperimental phase 2 risk factors, significantly (P≤.10) predicted CAA extent were added to the model. TPC-HDL cholesterol and insulin concentrations were significant predictors. Whereas both variables accounted for a significant proportion of the variance in CAA, both were independent of the effect of social status (initial social status×manipulated social status interaction, P=.008). Thus, none of the risk factors considered appears to mediate the effect of social status on CAA.

Discussion

The results of this study are congruent with the results of prior investigations. Previously it has been observed among females that were randomly assigned to social groups that those that were subordinate also had more extensive CAA than those that were dominant.1–3 The present experiment, if all females that were subordinate for the majority of the experiment (ie, subordinate for the majority of the experiment (ie, socially sensitive to the current social status of the individual that co-occurs with the initial social status of that individual. Altered social status increased blood pressure, irrespective of whether the females were dominant or subordinate in their final social groupings. Whereas the pattern of this effect was similar to the pattern of the effect of social status on CAA extent, SBP and DBP measured during experimental phase 2 were not significantly correlated with CAA extent.

Manipulated social status influenced ovarian function. Females that were socially subordinate during the 26 months in their manipulated social groups had lower mean peak luteal-phase plasma progesterone concentrations. In general, luteal-phase progesterone concentrations are indicative of the quality of the menstrual cycle, with higher concentrations indicating normal ovulatory cycles and lower concentrations indicating impaired menstrual cycles that may be anovulatory or characterized by abnormally low sex hormone concentrations.17,18 In prior experiments in which females were placed in social groups randomly without respect to their social status, subordinates had impaired ovarian function and exacerbated CAA. From these experiments, it was not possible to determine whether social status made an independent contribution to CAA risk. In the present experiment, ovarian function was especially sensitive to the current social status of the individual. Current subordinates had lower hormone concentrations than current dominants, irrespective of whether they had changed rank or not. Because CAA was worsened by a change in social status, whether to a subordinate or a dominant position, changing social status disassociated atherosclerosis extent from ovarian function. Thus, in the present experiment, social status had an effect on CAA independent of ovarian function.

Values of risk factors during the experiment, specifically plasma cholesterol and insulin concentrations in experimental phase 2, were significantly correlated with CAA extent; however, none of these appeared to be affected by initial or manipulated social status or changing social status.

Social subordination is thought to be a stressor and therefore deleterious to the health of monkeys. The assumption that subordinates are stressed is based on the observations that subordinates receive more aggression, spend more time alone, hypersecrete cortisol, and have suppressed reproductive function relative to dominants. The results of the present study suggest that it is
also deleterious to health to change social status. Previous observations suggest that social status is a reliable characteristic of the animal that is expressed similarly in different social environments. Compelling an animal to behave in an uncharacteristic fashion, whether by making dominants subordinate or subordinates dominant, may be stressful. The mechanism of the effect of changing social status on CAA is unknown. The results of this experiment suggest that it was not due to social status effects on lipid or carbohydrate metabolism, blood pressure, reproductive function, or body size or composition. Other possible mechanisms yet to be considered include vasomotor, heart rate, and blood pressure reactivity as well as other systems known to be stress responsive, such as the hypothalamic-pituitary-adrenal axis.

The modification of physiological risk factors, such as plasma cholesterol concentrations, results in lowered risk in humans. The efficacy of psychosocial risk factor modification (such as the modification of coronary-prone behavior pattern) is less certain. In the present study, an established psychosocial risk factor for female monkeys was modified, and this change was not effective in reducing CAA. An important aspect of the relationship between psychosocial stress and CAA may be the congruity between an individual's behavior and the psychosocial environment. Psychosocial risk factor modification may be a difficult undertaking because it is an attempt to alter a complex interaction between individuals and their psychosocial environment.

Acknowledgments

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References


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